AJOPAA 80 (1) 1-176 (1975)

VOLUME 80 NUMBER 1 JULY, 1975

AMERICAN JOURNAL OF OPHTHALMOLOGY

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*Drance, S.M. and Flindall, R.J.; Canad. J. of Ophth. *1:* #4:292-296, Oct. 1966.

AMERICAN JOURNAL

OF

OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON.

VOLUME 80

JULY-DECEMBER, 1975

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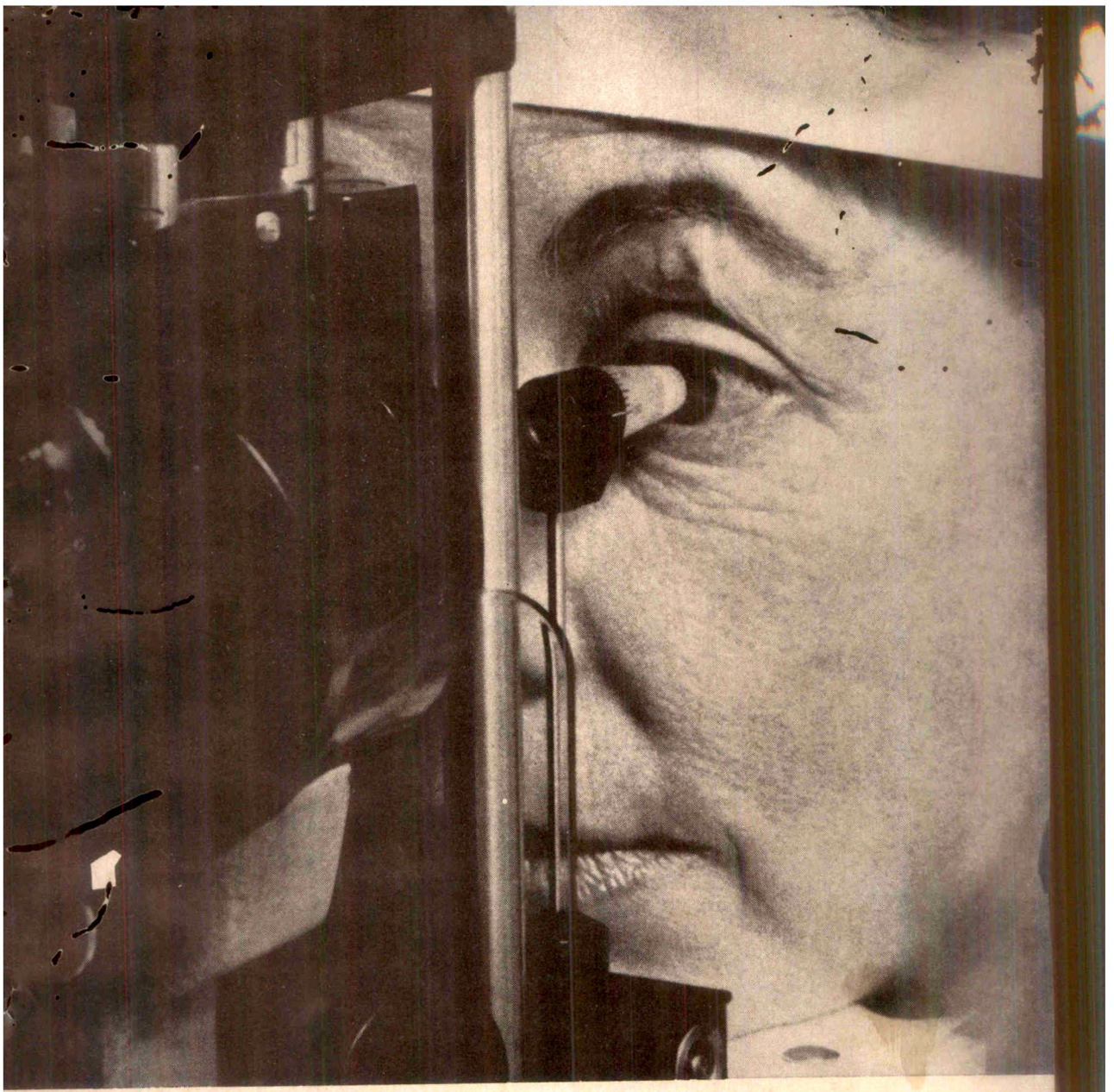
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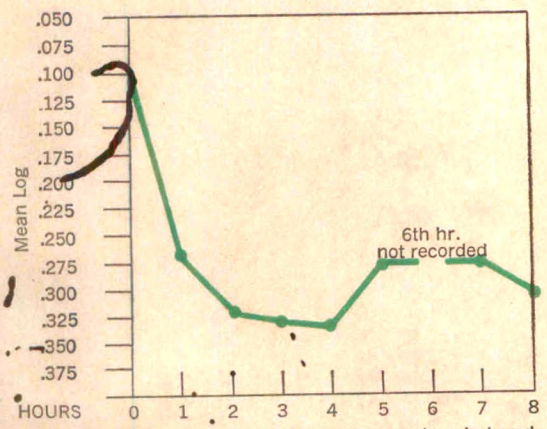
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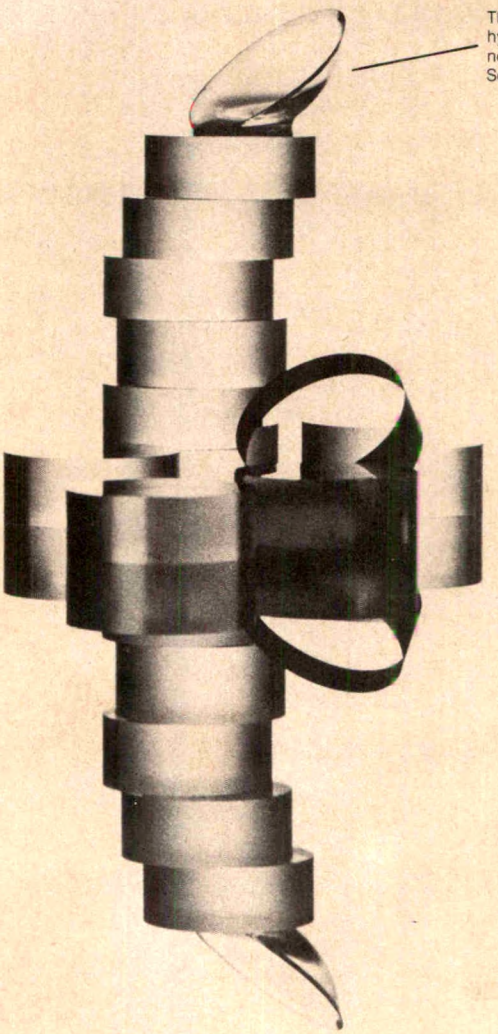
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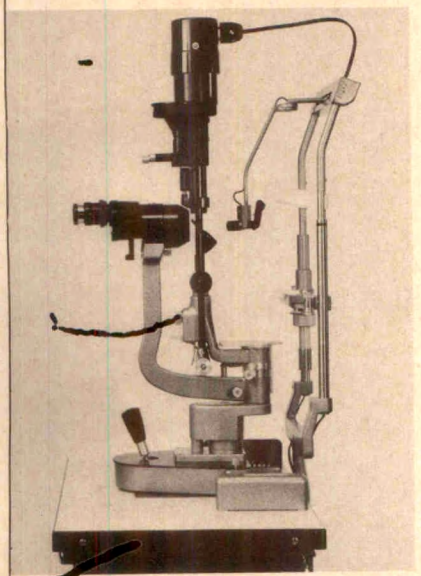
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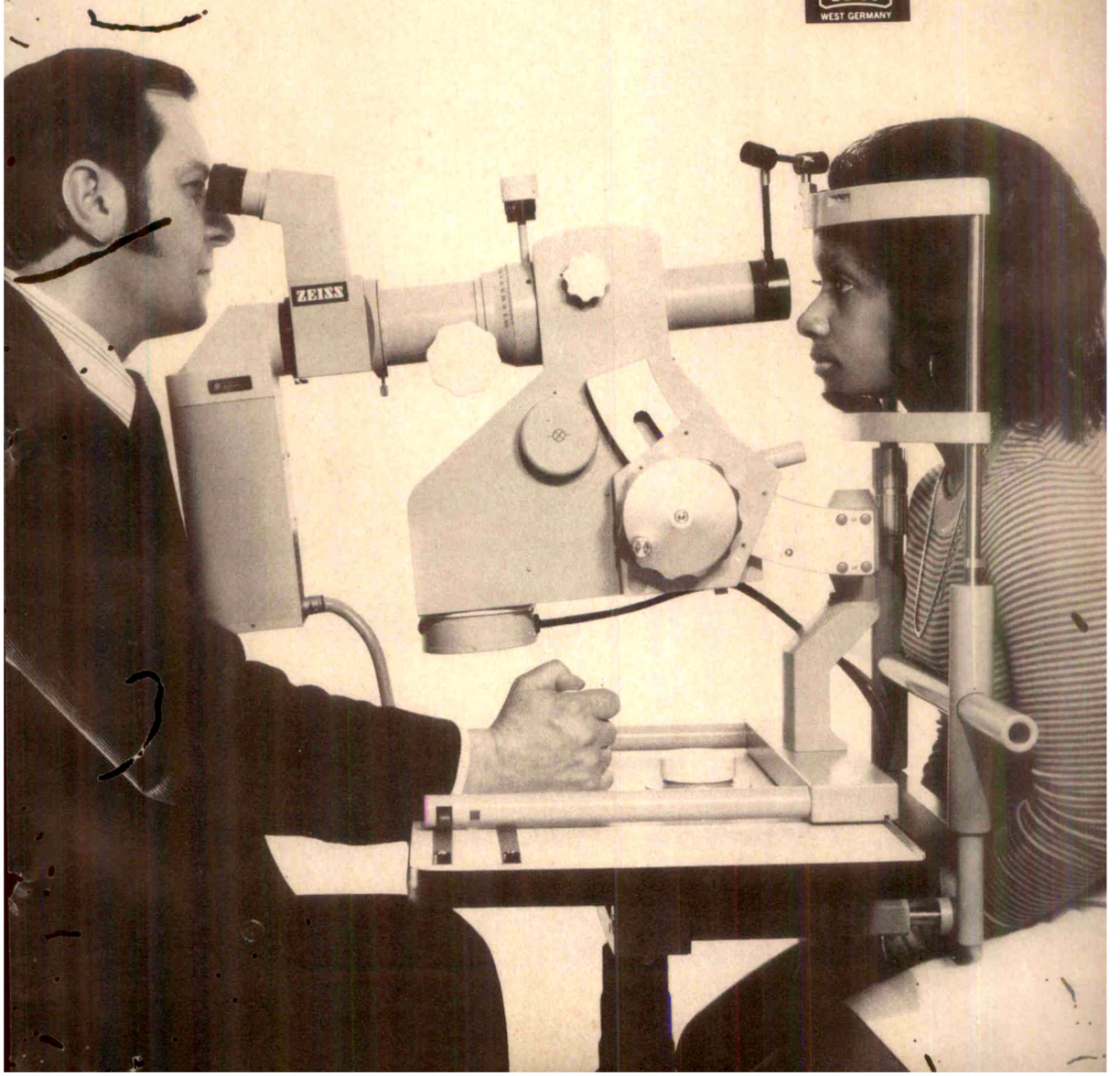
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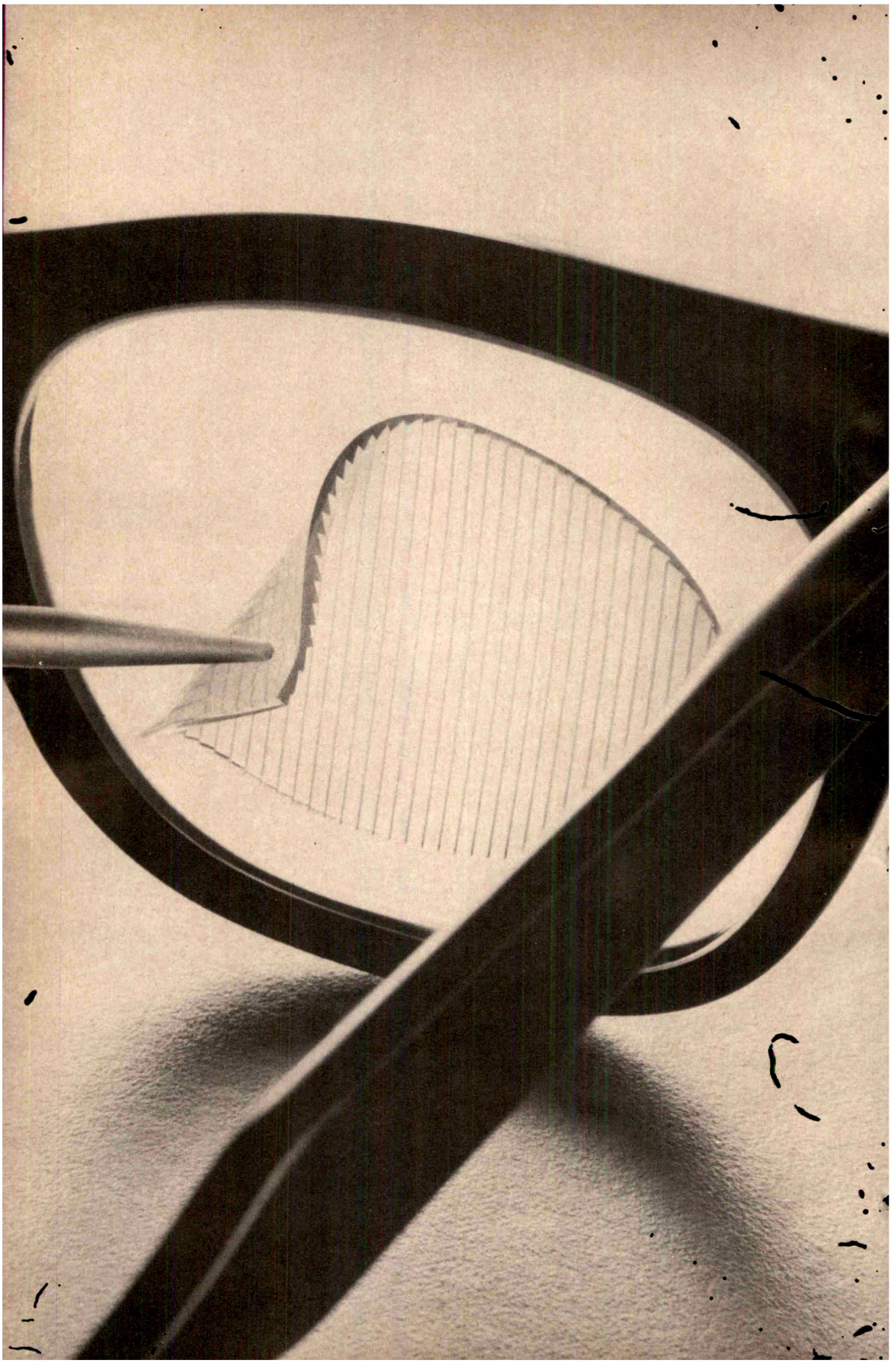
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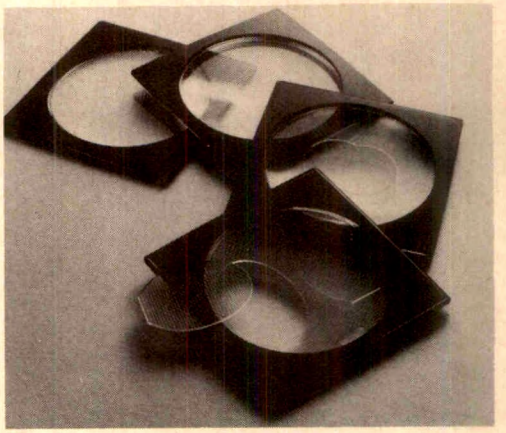
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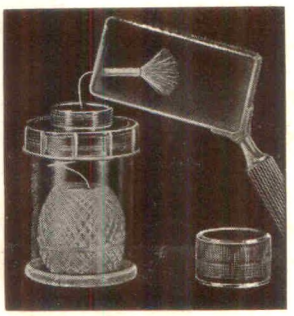
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The basic rationale behind the use of potent ophthalmic steroids such as FML and Pred Forte is to maintain functional integrity of the eye. In general, as long as evidence of active inflammation persists, it may be hazardous to discontinue steroid therapy. Use of potent steroids may in fact help preserve the ocular structure.[1]

When not to use potent steroids. Despite their usefulness, there are times when potent steroids (and mild ones too, for that matter) should be used with extreme caution – or not at all. It is generally agreed that untreated purulent infections, most viral diseases and ocular fungal infestations should be considered as contraindications to the use of these agents.

Indications and methods of use. Either FML or Pred Forte may be used to treat moderately severe to severe steroid responsive inflammatory conditions such as iritis, uveitis, iridocyclitis, episcleritis and resistant ocular allergy. In addition, data[2] made available recently attest to the usefulness of FML in long-term treatment of inflammation following cataract removal and keratoplasty. The patient photos to the right demonstrate the effectiveness of both FML and Pred Forte in severe ocular inflammation.

The usual method of administering either FML or Pred Forte is to instill one or two drops into the conjunctival sac two to four times a day. But to provide maximum therapeutic effectiveness when the severity of the inflammation dictates, the dosage can be *safely* increased to two drops every hour during the first 24 to 48 hours.

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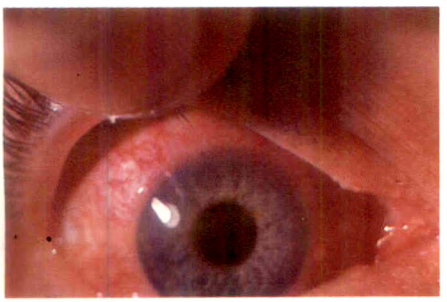
ACTIONS Inhibition of the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. Adrenocorticosteroids and their derivatives are capable of producing a rise in intraocular pressure. In clinical studies on patients' eyes treated with both dexamethasone and fluorometholone, fluorometholone demonstrated a lower propensity to increase intraocular pressure than did dexamethasone. **INDICATIONS** For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **CONTRAINDICATIONS** Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **WARNINGS** Steroid medication in the treatment of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by presence of steroid medication. Safety and effectiveness have not been demonstrated in children of the age group 2 years or below. Use In Pregnancy: Safety of the use of topical steroids during pregnancy has not been established. **PRECAUTIONS** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intraocular pressure should be checked frequently. **ADVERSE REACTIONS** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe. **DOSAGE AND ADMINISTRATION** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

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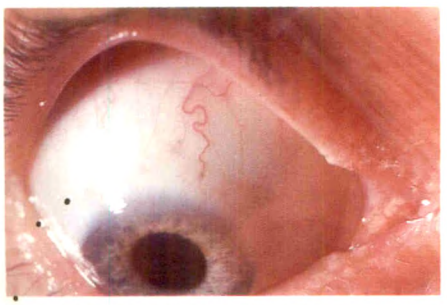
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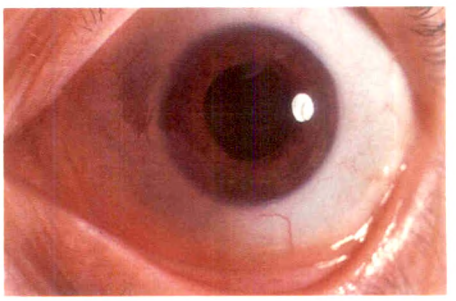
Patient CH. White male. Age 46. Acute episcleritis secondary to rheumatoid arthritis. Treatment started 2/24: FML one drop every hour for 48 hours then one drop every two hours for 36 hours then one drop every four hours thereafter.



Patient LV. White male. Age 57. Acute episcleritis. Treatment started 2/27: Pred Forte one drop every hour for 48 hours then one drop every two hours for 36 hours then one drop every four hours thereafter; warm compresses and scopolamine ointment twice daily.



Patient CH on 3/9. FML therapy stopped.



Patient LV on 3/12. Pred Forte therapy stopped.

References

1. Leopold, I.H. The steroid shield in ophthalmology, Trans Amer Acad Ophth & Oto 71:273–289, 1967.

2. Castroviejo, R. Data presented at 79th American Academy of Ophthalmology and Otolaryngology, Dallas, Oct. 1974.

3. Leibowitz, Howard M., Data presented at 79th American Academy of Ophthalmology and Otolaryngology, Dallas, Oct. 1974.

Photos by Dr. Ira Abrahamson, Cincinnati, Ohio

Pred Forte® (prednisolone acetate) 1% Sterile Ophthalmic Suspension

INDICATIONS For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **CONTRAINDICATIONS** Acute untreated purulent ocular infections, acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, ocular tuberculosis, and fungal diseases of the eye, and sensitivity to any components of the formulation. **WARNINGS** 1. In those diseases causing thinning of the cornea, perforation has been reported with the use of topical steroids. 2. Since PRED FORTE® contains no antimicrobial, if infection is present appropriate measures must be taken to counteract the organisms involved. 3. Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids. 4. Use of steroid medication in the presence of stromal herpes simplex requires caution and should be followed by frequent mandatory slit-lamp microscopy. 5. As fungal infections of the cornea have been reported coincidentally with long-term local steroid applications, fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use. 6. Use of topical corticosteroids may cause increased intraocular pressure in certain individuals. This may result in damage to the optic nerve with defects in the visual fields. It is advisable that the intraocular pressure be checked frequently. 7. Use in Pregnancy – Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. **PRECAUTIONS** Posterior subcapsular cataract formation has been reported after heavy or protracted use of topical ophthalmic corticosteroids. Patients with histories of herpes simplex keratitis should be treated with caution. **ADVERSE REACTIONS** Increased intraocular pressure, with optic nerve damage, defects in the visual fields. Also posterior subcapsular cataract formation, secondary ocular infections from fungi or viruses liberated from ocular tissues, and perforation of the globe when used in conditions where there is thinning of the cornea or sclera. Systemic side effects may occur with extensive use of steroids. **DOSAGE AND ADMINISTRATION** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

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British Journal of Ophthalmology

February 1975 Vol. 59 No. 2

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Silastic rod encirclement in retinal detachment surgery. *A Zayed, B. Shalash and P. Amalric*

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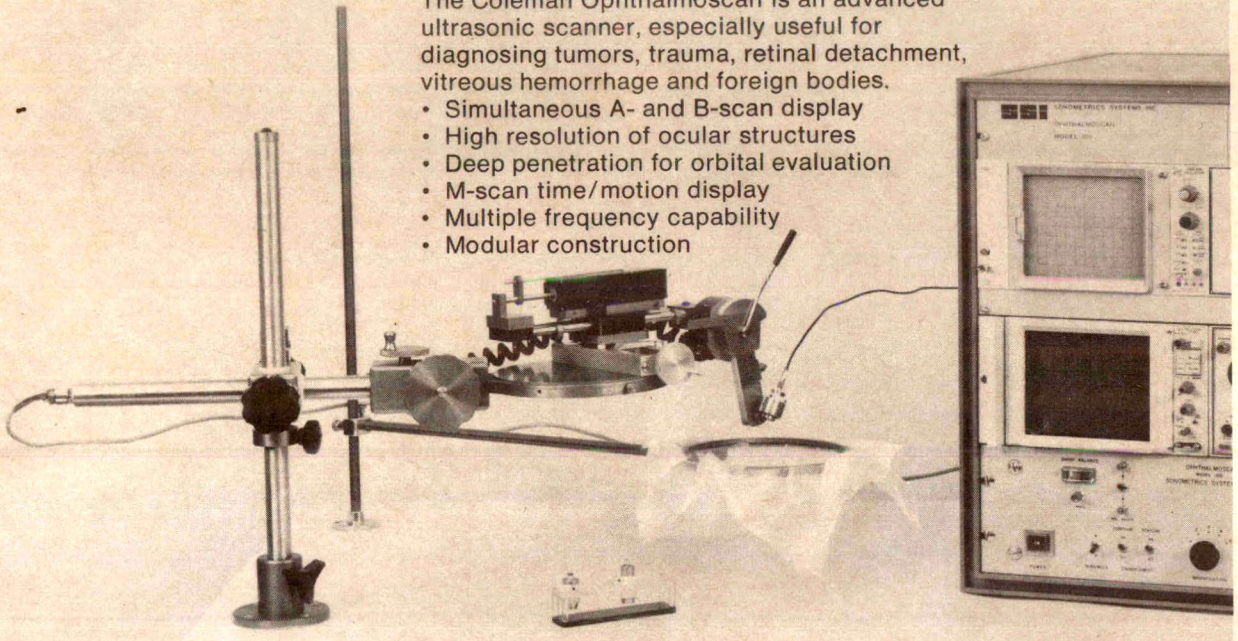
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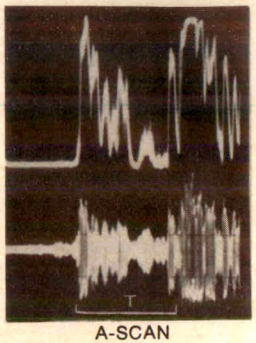
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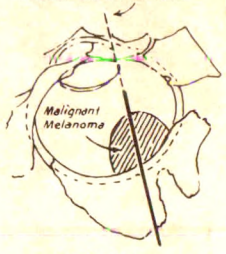
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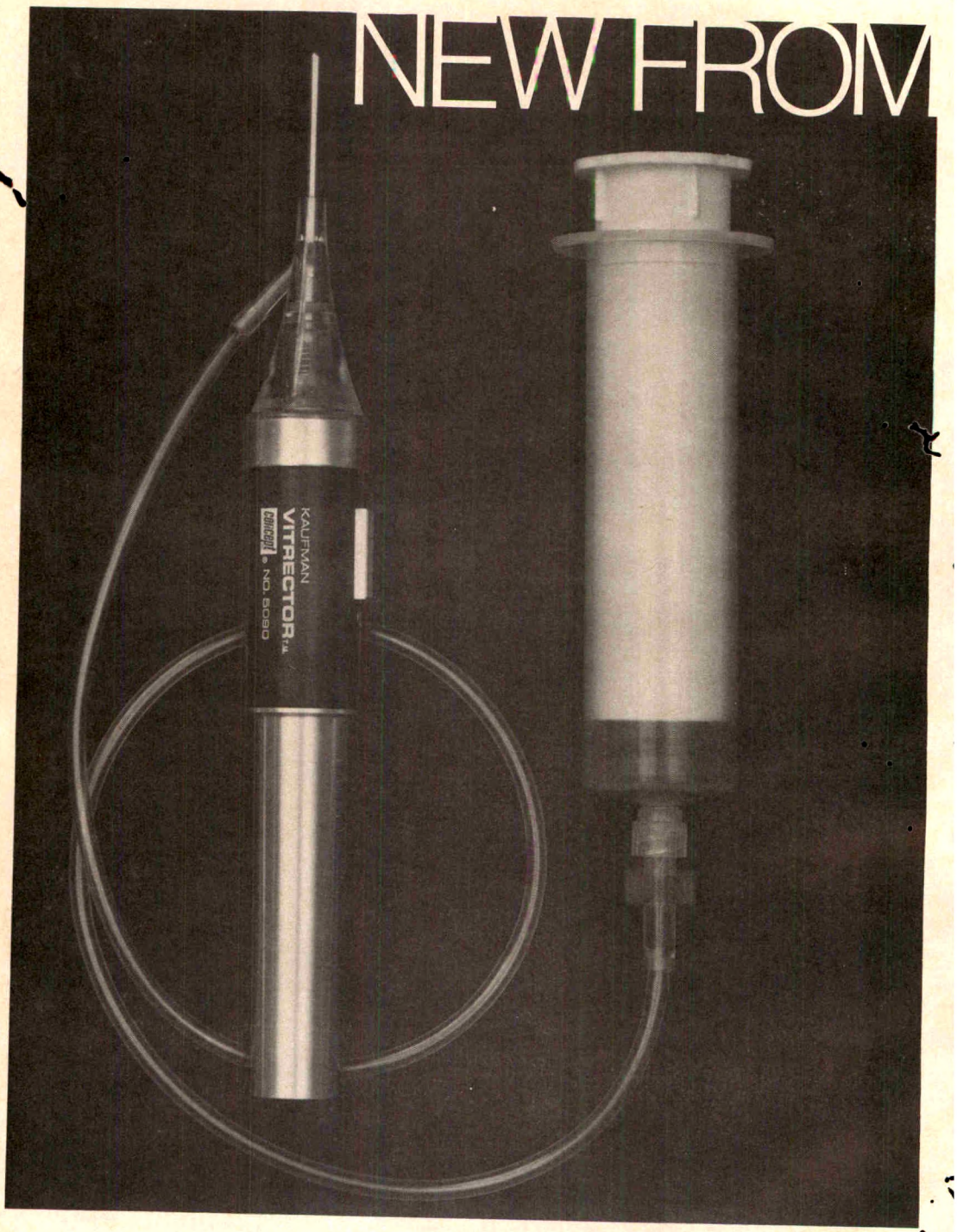


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See: Ultrasonic Diagnosis of Tumors of the Choroid-Arch Ophthalmol/Vol. 91, May 1974

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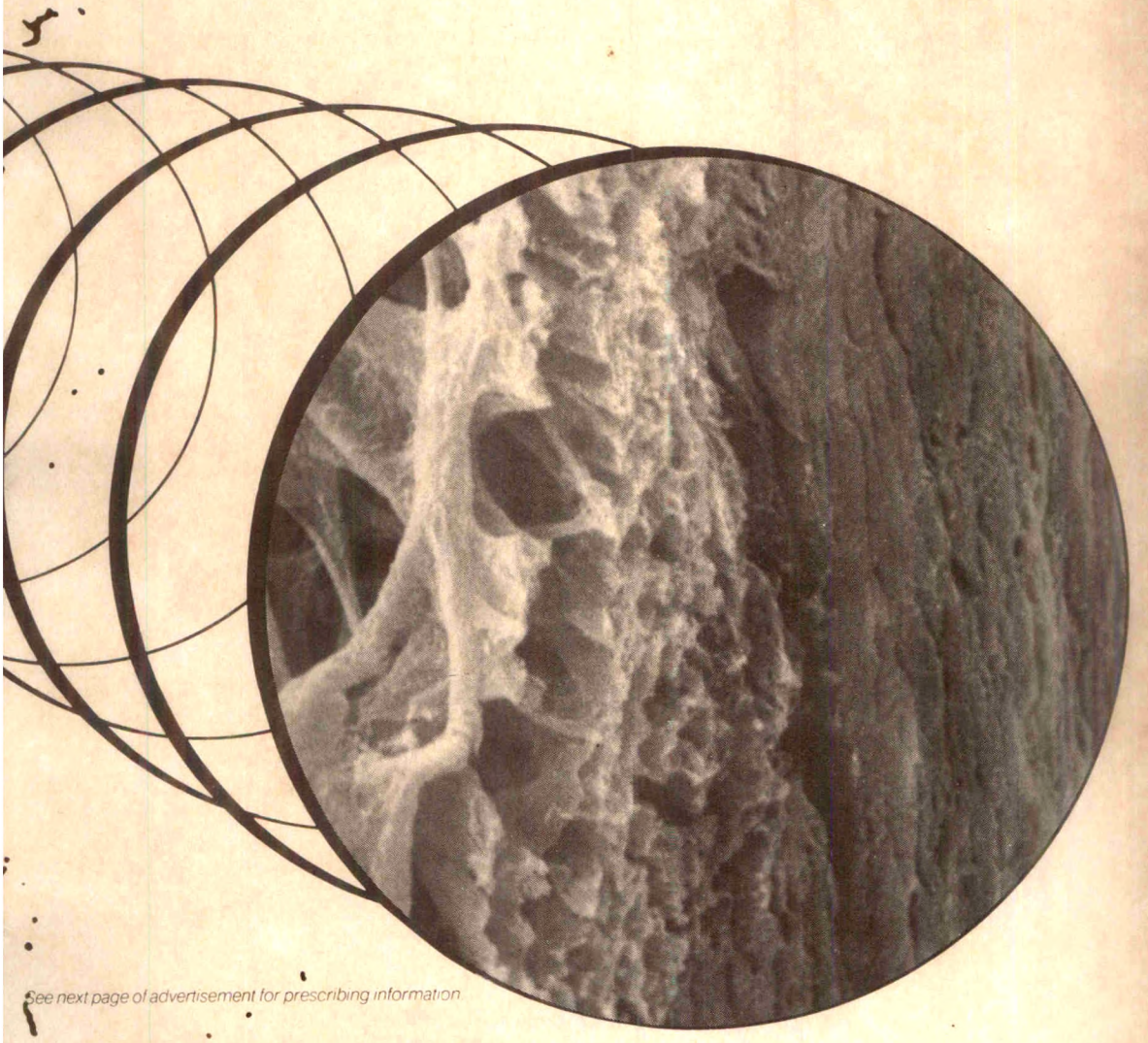
Because PHOSPHOLINE IODIDE is long-acting, it can help provide uninterrupted control of intraocular pressure in chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia. Just one or, at most, two instillations of PHOSPHOLINE IODIDE (one at bedtime, and, if necessary, one in the morning) are generally needed.

Although PHOSPHOLINE IODIDE is longer-acting than other miotics, it is *not* more potent. With four concentrations available, it offers a high degree of dosage flexibility for uninterrupted control of intraocular pressure...used alone or in combination with other medication.

When starting PHOSPHOLINE IODIDE therapy, 0.03%—the lowest strength—is the logical choice. If strengths of 0.06%, 0.125%, or 0.25% are required, the initial use of the 0.03% will be helpful in smoothing the transition.

PHOSPHOLINE IODIDE® not more potent... but longer-acting

(echothiophate iodide for ophthalmic solution)



See next page of advertisement for prescribing information

PHOSPHOLINE IODIDE®
(echothiophate iodide)
in the management of chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia

BRIEF SUMMARY
(*For full prescribing information, see package circular.*)
PHOSPHOLINE IODIDE® (echothiophate iodide)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia—Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

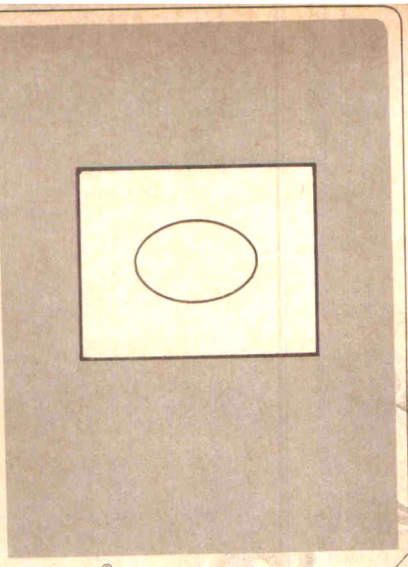
7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.]

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The Ophthalmos Division
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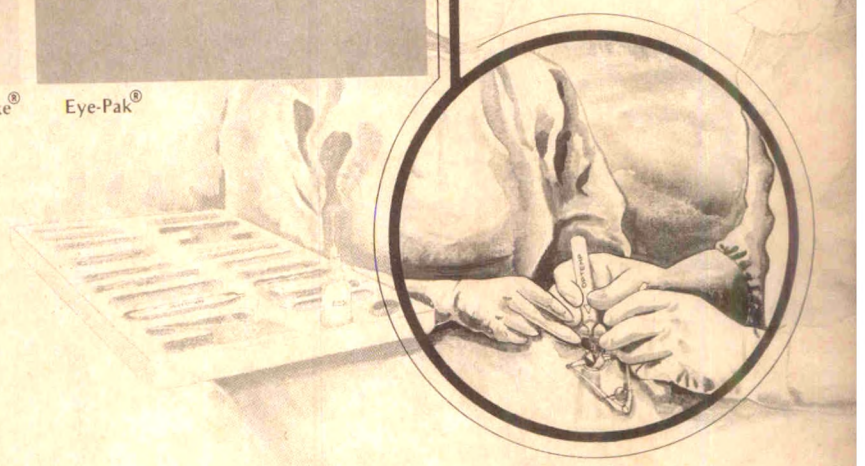
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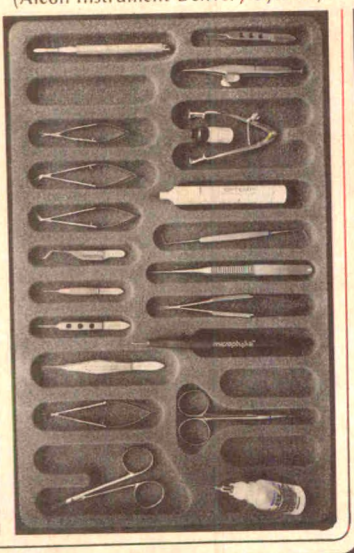
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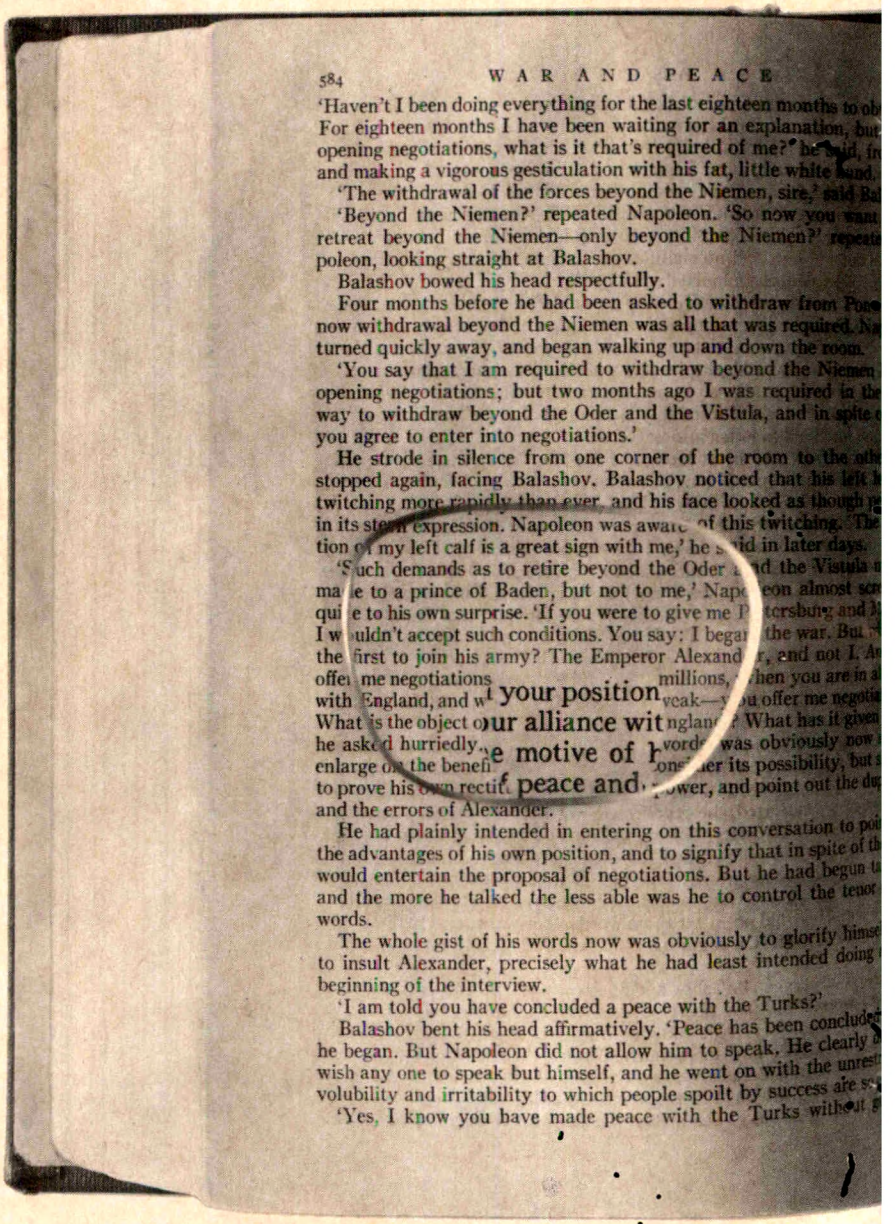
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THE WI



584 WAR AND PEACE

'Haven't I been doing everything for the last eighteen months to ob
For eighteen months I have been waiting for an explanation, but
opening negotiations, what is it that's required of me?' he said, fr
and making a vigorous gesticulation with his fat, little white hand.

'The withdrawal of the forces beyond the Niemen, sire,' said Ba

'Beyond the Niemen?' repeated Napoleon. 'So now you want
retreat beyond the Niemen—only beyond the Niemen?' repeat
poleon, looking straight at Balashov.

Balashov bowed his head respectfully.

Four months before he had been asked to withdraw from Pom
now withdrawal beyond the Niemen was all that was required. Na
turned quickly away, and began walking up and down the room.

'You say that I am required to withdraw beyond the Niemen
opening negotiations; but two months ago I was required in the
way to withdraw beyond the Oder and the Vistula, and in spite o
you agree to enter into negotiations.'

He strode in silence from one corner of the room to the oth
stopped again, facing Balashov. Balashov noticed that his left l
twitching more rapidly than ever, and his face looked as though
in its stern expression. Napoleon was aware of this twitching. The
tion of my left calf is a great sign with me,' he said in later days.

'Such demands as to retire beyond the Oder and the Vistula
make to a prince of Baden, but not to me,' Napoleon almost scr
quite to his own surprise. 'If you were to give me Petersburg and
I wouldn't accept such conditions. You say: I began the war. But
the first to join his army? The Emperor Alexander, and not I. An
offer me negotiations millions, when you are in a
with England, and w your position veak—you offer me negotia
What is the object our alliance wit ngland? What has it given
he asked hurriedly, e motive of h vorder was obviously now
enlarge on the benefi onsider its possibility, but
to prove his own rectit peace and ower, and point out the du
and the errors of Alexander.

He had plainly intended in entering on this conversation to poi
the advantages of his own position, and to signify that in spite of th
would entertain the proposal of negotiations. But he had begun t
and the more he talked the less able was he to control the tenor
words.

The whole gist of his words now was obviously to glorify himse
to insult Alexander, precisely what he had least intended doing
beginning of the interview.

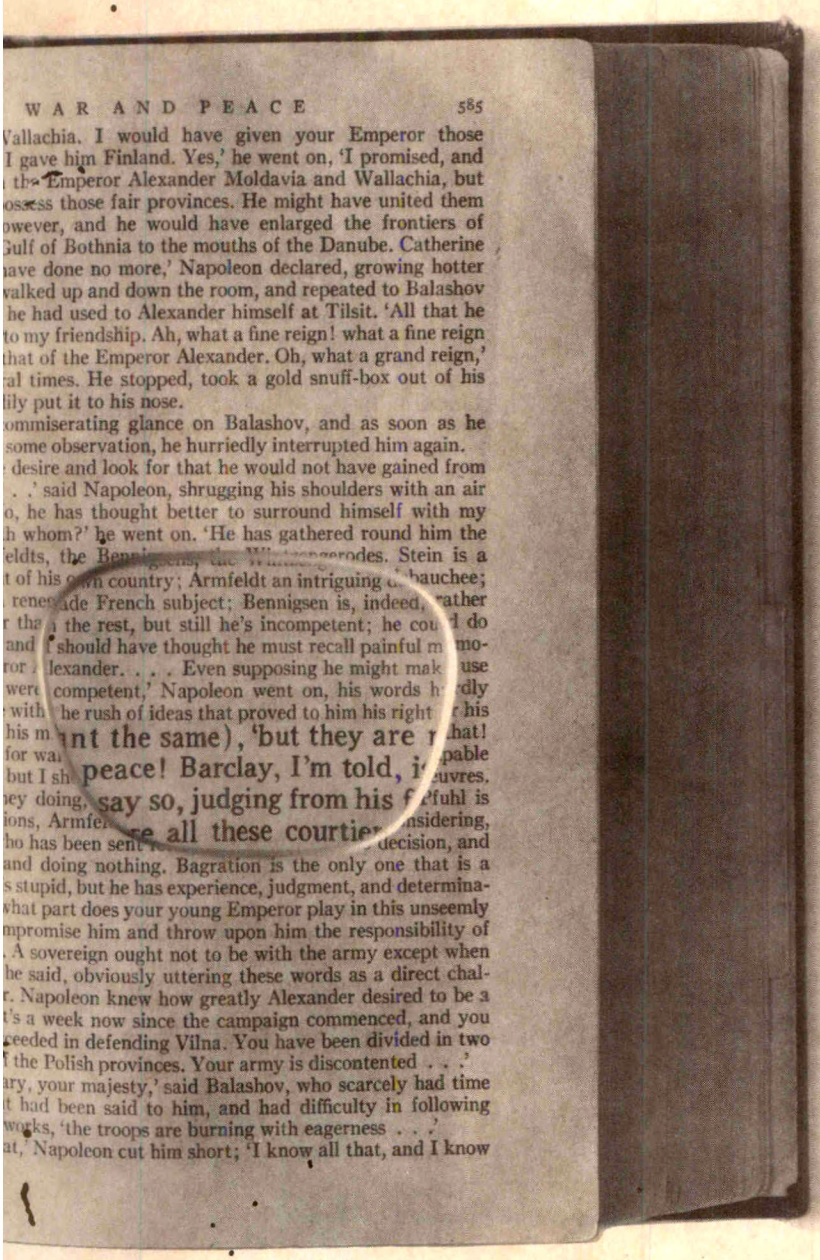
'I am told you have concluded a peace with the Turks?'

Balashov bent his head affirmatively. 'Peace has been concluded
he began. But Napoleon did not allow him to speak. He clearly d
wish any one to speak but himself, and he went on with the unres
volubility and irritability to which people spoilt by success are s

'Yes, I know you have made peace with the Turks without g

who never quite made it "War and Peace."

DE ONE.



WAR AND PEACE 585

Wallachia. I would have given your Emperor those
I gave him Finland. Yes,' he went on, 'I promised, and
the Emperor Alexander Moldavia and Wallachia, but
ossess those fair provinces. He might have united them
owever, and he would have enlarged the frontiers of
Gulf of Bothnia to the mouths of the Danube. Catherine
ave done no more,' Napoleon declared, growing hotter
valked up and down the room, and repeated to Balashov
he had used to Alexander himself at Tilsit. 'All that he
to my friendship. Ah, what a fine reign! what a fine reign
that of the Emperor Alexander. Oh, what a grand reign,'
al times. He stopped, took a gold snuff-box out of his
ily put it to his nose.
ommiserating glance on Balashov, and as soon as he
some observation, he hurriedly interrupted him again.
desire and look for that he would not have gained from
. .' said Napoleon, shrugging his shoulders with an air
o, he has thought better to surround himself with my
h whom?' he went on. 'He has gathered round him the
eldts, the Ben[illegible]
t of his own country; Armfeldt an intriguing d[illegible]bauchee;
renes[illegible]de French subject; Bennigsen is, indeed, rather
r tha[illegible] the rest, but still he's incompetent; he cou[illegible]d do
and [illegible] should have thought he must recall painful m[illegible]mo-
ror [illegible]lexander. . . . Even supposing he might mak[illegible]use
were [illegible] competent,' Napoleon went on, his words h[illegible]dly
with [illegible]he rush of ideas that proved to him his right [illegible]r his
his m[illegible]nt the same), 'but they are [illegible]hat!
for wa[illegible]pable
but I sh[illegible]peace! Barclay, I'm told, i[illegible]euvres.
ey doing, [illegible]say so, judging from his f[illegible]fuhl is
ions, Armfe[illegible]e all these courtie[illegible]nsidering,
ho has been sent [illegible] decision, and
and doing nothing. Bagration is the only one that is a
s stupid, but he has experience, judgment, and determina-
what part does your young Emperor play in this unseemly
mpromise him and throw upon him the responsibility of
. A sovereign ought not to be with the army except when
he said, obviously uttering these words as a direct chal-
r. Napoleon knew how greatly Alexander desired to be a
t's a week now since the campaign commenced, and you
ceeded in defending Vilna. You have been divided in two
the Polish provinces. Your army is discontented . . .'
ary, your majesty,' said Balashov, who scarcely had time
t had been said to him, and had difficulty in following
works, 'the troops are burning with eagerness . . .'
at,' Napoleon cut him short; 'I know all that, and I know

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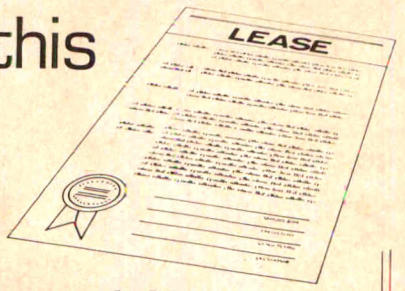
The Wide One offers the greatest flexibility in positioning and fitting of bifocal lenses.

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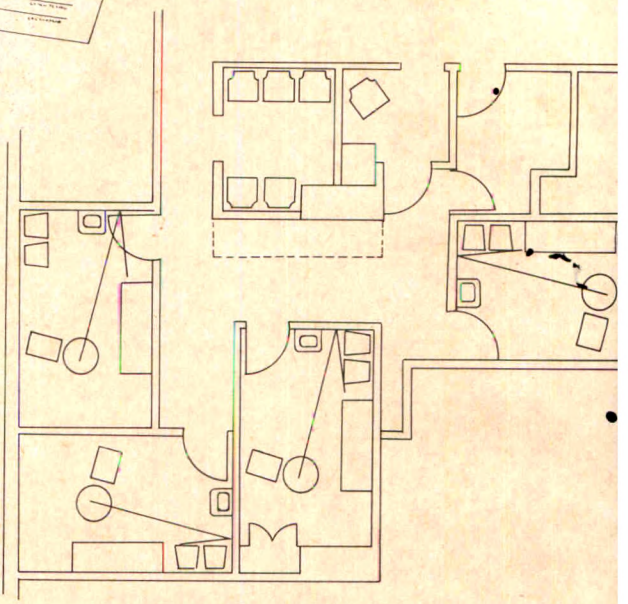
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(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)

in the diagnosis and treatment of accommodative esotropia

BRIEF SUMMARY
(For full prescribing information, see package circular.)

PHOSPHOLINE IODIDE®
(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)
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Indications: 1. Glaucoma – Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia – Concomitant esotropias with a significant accommodative component.

Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.

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2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

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6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

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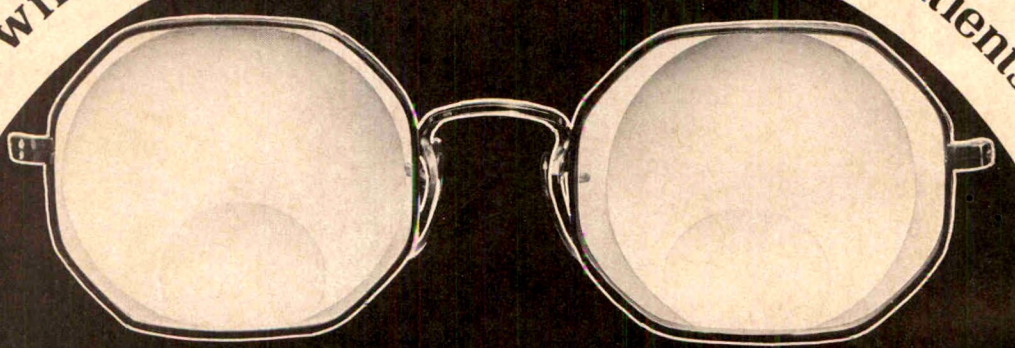
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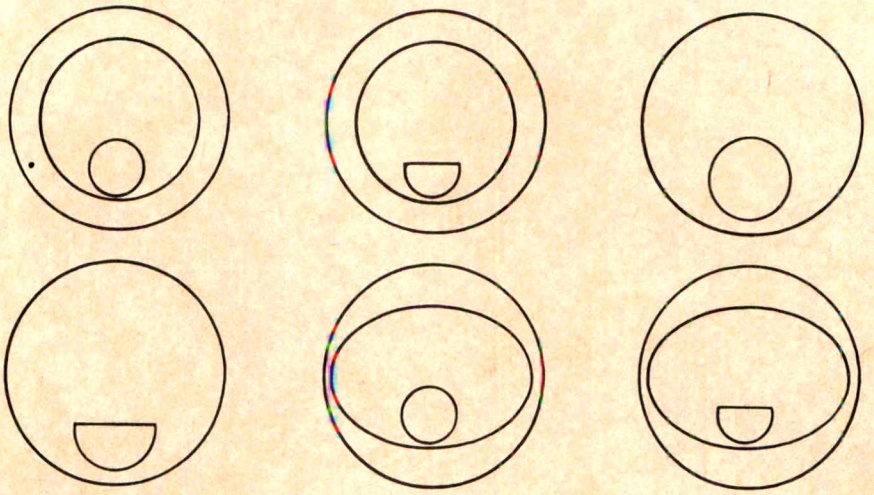
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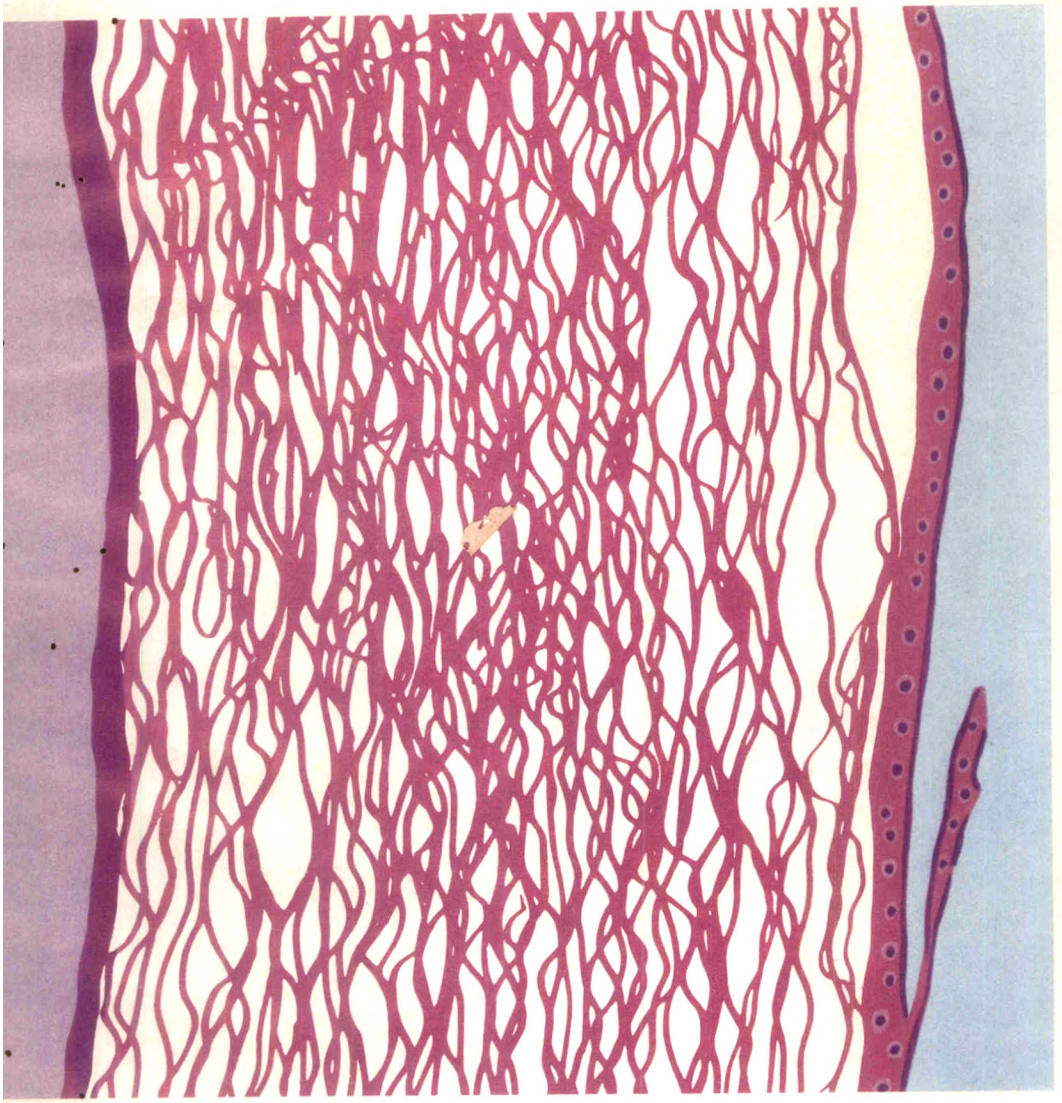
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Clinical studies conducted by 21 ophthalmologists in hospitals and private clinical practices confirm SOFLENS® (polymacon) Contact Lens effectiveness in relieving the pain of bullous keratopathy. Of 348 patients, 269 or 77.3% experienced relief from pain following application of the lens. Seventy-nine patients or 22.7% were unsuccessful in wearing the lens. The primary reasons given for lack of success were poor tolerance, discomfort, no change in symptoms, poor visual acuity, or poor fit.

Therapeutic Advances:

Now SOFLENS Contact Lenses are recommended for relief of the painful symptoms of bullous keratopathy. Although all lens series (B, F, J, N, C, and T) may be utilized as transparent barriers to protect the cornea from eyelid friction, the new plano T series is particularly well suited for this therapeutic application.

Because the T lens is large (14.7mm), relatively thin (.18mm), and fits comfortably on most eyes, it should be the lens of first choice.

Therapeutic Advantages:

The SOFLENS Contact Lens is biologically and chemically inert, dimensionally stable, and reliable. These qualities which make the lens a lens of choice in vision correction, when indicated, now provide an effective modality to aid the physician in meeting his therapeutic goals. Placement of the lens generally results in rapid pain relief for the patient.

Therapeutic Convenience:

Medication with preservatives may be used in the usual dosage regimens when indicated. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens. Since all SOFLENS Contact Lens series and powers are available for the treatment of bullous keratopathy, vision correction may also be possible.

SOFLENS Contact Lenses are contraindicated in the presence of any active, untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

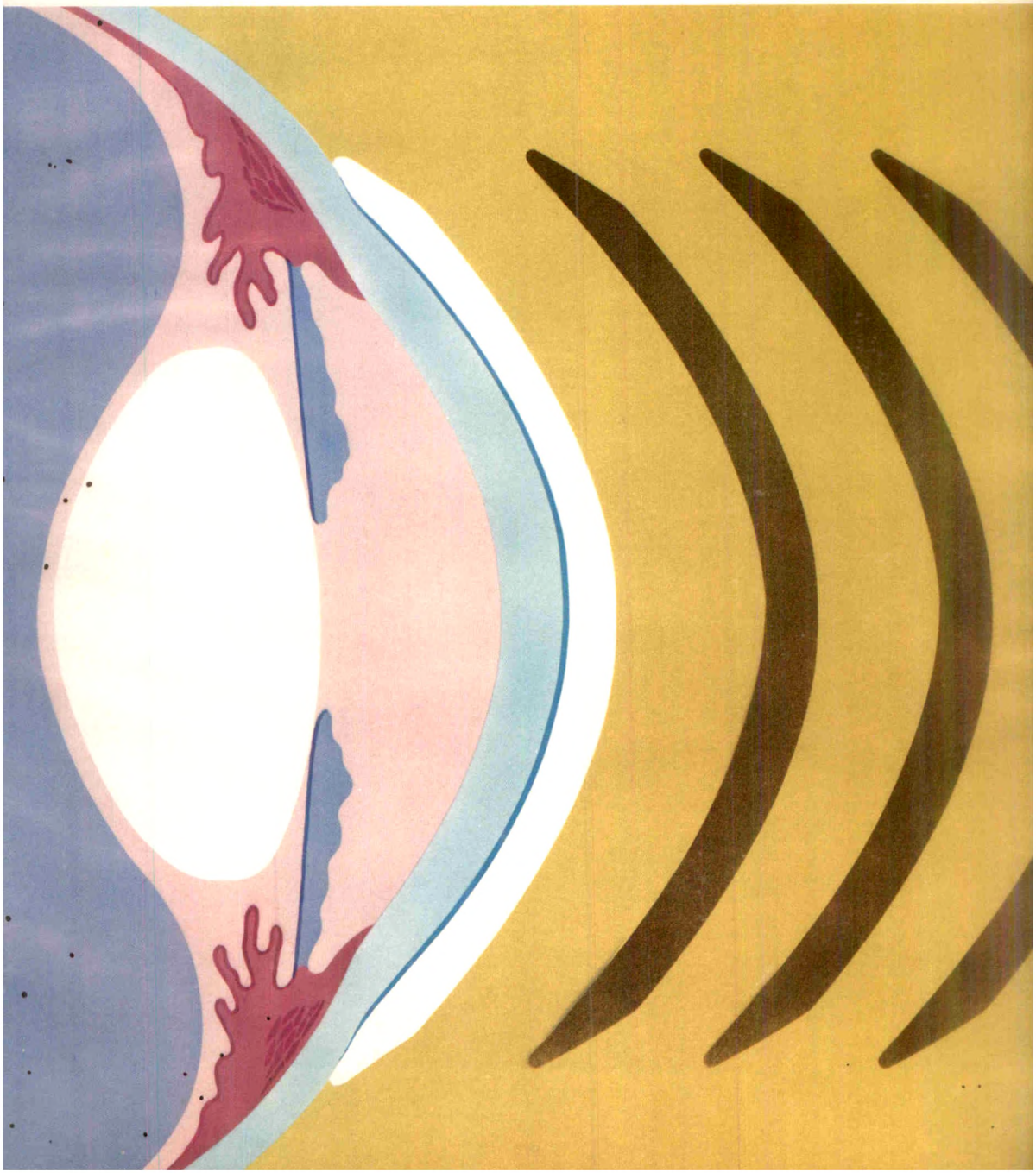
SOFLENS Contact Lenses are easily applied by the physician. Because of flexibility and thin edges of the lenses, most patients adjust to them quickly. While the patient's pain is controlled, the physician gains time to consider other therapeutic procedures. Thus, the SOFLENS Contact Lens preserves future therapeutic options.

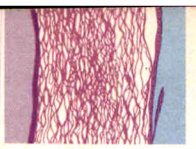
*Data on file at Bausch & Lomb Incorporated. Available on request.

For Bullous Keratopathy you can prescribe with confidence

soflens®
(polymacon)
CONTACT LENS.

For therapeutic application, choose the new plano T series or... the B, F, J, N, and C SOFLENS Contact Lens series.





SOFLENS (polymacon) CONTACT LENS

THERAPEUTIC USE

DESCRIPTION: The SOFLENS® (polymacon) Contact Lens is a hemispherical flexible shell which covers the cornea and may cover a portion of the adjacent sclera. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The material has a refractive index of 1.43 and the lens has a visible light transmittance of more than 97%.

ACTIONS: In its hydrated state a SOFLENS Contact Lens is soft and pliable. When placed on the human cornea, the hydrated SOFLENS Contact Lens acts as a refracting medium to compensate spherical ametropias and as a pain reliever by providing a well tolerated barrier between the exposed corneal nerves and the lids.

INDICATIONS: SOFLENS® (polymacon) Contact Lenses may be useful in the treatment and management of painful bullous keratopathy.

CONTRAINDICATIONS: SOFLENS Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

WARNINGS: Patients should be instructed to consult their physician if the eye becomes uncomfortable or irritated. If undue delay is anticipated, the lens should be removed immediately and stored in normal saline.

SOFLENS Contact Lenses must not be used in combination with solutions commonly used for cleaning, wetting and storage of hard contact lenses as these will produce severe corneal irritation.

The patient should be instructed to use only eyedrops prescribed by the physician when the lens is on the eye.

Medication with preservatives may be used when indicated in the usual dosage regimens. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens.

Deposits, which frequently occur on the lens with continuous wear, may cause discomfort and necessitate replacement as often as every two or three months.

SOFLENS® (polymacon) Contact Lenses should not be used in the presence of noxious and irritating vapors. Safety in pregnancy has not been substantiated. Insufficient lacrimal secretion or hypoesthesia may be restricting factors to the wearing of soft contact lenses.

Malfunction and rusting of the metal interior of the Aseptor®–Patient Unit as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure.

Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses.

PRECAUTIONS: Placement and Removal–SOFLENS® (polymacon) Contact Lenses should be applied and removed only by the physician. However, all patients should be instructed in the techniques of placing and removing a lens, so they can do so should it become necessary.

When the SOFLENS Contact Lens is used for the treatment of painful bullous keratopathy, it is to be worn continuously, for 24 hours a day, following the initial application. The patient should be followed closely during the initial stages of treatment. The lens should be comfortable and the pain of bullous keratopathy should be relieved almost immediately. If the lens is not comfortable and pain persists, another lens should be tried for appropriate fit.

Daily placement and removal of the lens by the patient may be permitted. However, if daily removal increases the risk of additional damage to the already compromised corneal epithelium and when the degree of pain relief is significant during the time the lens is worn, continuous wear should be employed.

Storage–SOFLENS® (polymacon) Contact Lenses must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in normal saline solution until it returns to its soft, pliable state which may take as long as forty minutes.

Fresh normal saline must be prepared for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The one ounce squeeze bottle is intended for preparation of normal saline only. As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected.

Hygiene–Hands must be washed, rinsed thoroughly, and dried with a lint-fr towel before handling the lenses.

Cosmetics, lotions, soaps, and creams must not come in contact with the lens since eye irritation may result. If hair spray is used while the lenses are bei worn, the eyes must be kept closed until the hair spray has settled.

Handling–A SOFLENS® (polymacon) Contact Lens may be damaged by nicking tearing if care is not exercised during placement on or removal from the e replacing or removing it from the carrying case or in the cleaning process. Lens must be placed very carefully in the carrying case to avoid damaging the edges the lenses.

Disinfecting–Fresh normal saline must be prepared daily. After removal from t eye, the SOFLENS® (polymacon) Contact Lens must be irrigated with saline a rubbed gently to remove mucus and film from the lens' surface. The carrying ca must be emptied and refilled with fresh normal saline solution just befo disinfecting the lenses.

The SOFLENS Carrying Case should be washed at least once a week with h water and then rinsed thoroughly with distilled water. Soap or other cleane should never be used to clean the carrying case.

Disinfecting with the SOFLENS Aseptor®–Patient Unit is necessary to k microorganisms.

If a SOFLENS Aseptor is not available, the lenses may be disinfected by boili them in their carrying case in a pan of water for 15 minutes. When this boili method of disinfection is used, the lenses can be damaged if the boiling water allowed to completely evaporate.

The carrying case must always be tightly closed before disinfecting to preve leakage of the saline from the case and subsequent dehydration of the lens

Fluorescein–Never use fluorescein while the patient is wearing the lens because the lenses will become discolored. Whenever fluorescein is used, flu the eyes with sterile normal saline solution and wait at least one hour bef replacing the lenses. Earlier replacement may cause the lenses to absorb residu fluorescein.

ADVERSE REACTIONS: Infiltrates, neovascularization, and corneal ulcers ha been reported.

Serious corneal damage may result from wearing a SOFLENS® (polymaco Contact Lens which has been soaked in a conventional contact lens solution.

Eye irritation may occur within a short time after putting on a hypertonic le Removal of the lens will relieve the irritation.

A lens adheres very rarely to an eye as a result of sleeping with the lens on wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline a wait until the lens moves freely before removing it.

A faint blue haze, believed to be located in Descemet's membrane, has be reported in the Spokane, Washington area in approximately 26 wearers w otherwise normal eyes. As yet, the cause is unknown and the phenomenon has n been found elsewhere. The wearers report no subjective symptons and there is detectable effect on their visual acuity.

HOW SUPPLIED: Each lens is supplied sterile in a glass vial containing ster normal saline solution. The glass vial is marked with the manufacturing number of the lens and the dioptric power (black for plus power lenses; red minus; gold for plano).

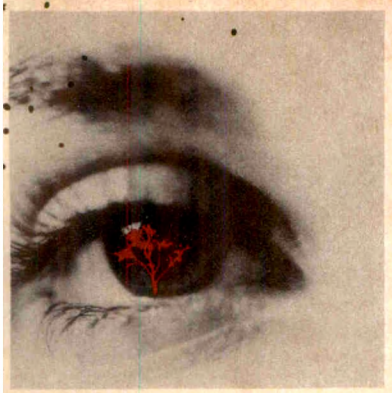
The SOFLENS Care Kit is available for lens disinfecting, cleaning and storag consisting of the following:

SOFLENS Carrying Case	Cat. #140301
SOFLENS Aseptor®–Patient Unit	Cat. #140302
SOFLENS Squeeze Bottle	Cat. #140304
SOFLENS Salt Tablets	Cat. #140305
SOFLENS Patient Instruction Book	Cat. #140300-1

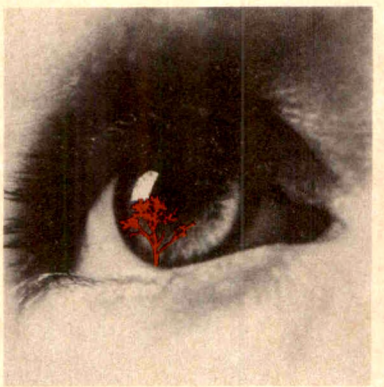
Caution: Federal Law Prohibits Dispensing Without a Prescription

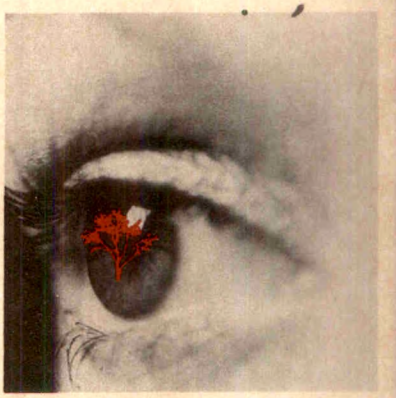
MARCH 1975

BAUSCH & LOMB
SOFLENS DIVISION
Rochester, N.Y. 14602









Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Only in the treatment of herpes simplex keratitis.

Description: 'Stoxil' Ophthalmic Solution contains idoxuridine (5-iodo-2-deoxyuridine) 0.1% (1 mg./ml.) in distilled water; sterile when packaged. Preserved with thimerosal, 1:50,000. 'Stoxil' Ophthalmic Ointment contains idoxuridine 0.5% (5 mg./gram) in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

Contraindications: Contraindicated in patients with known or suspected hypersensitivity to any of its components.

Warning: Usage in Pregnancy—Idoxuridine should be administered with caution in pregnancy or in women of childbearing potential. Although teratogenic effects were reported in one study with rabbits when idoxuridine was instilled into the eye, these effects were not observed in a subsequent, more detailed study, even at doses substantially higher than those in the preceding study.

Precautions: Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

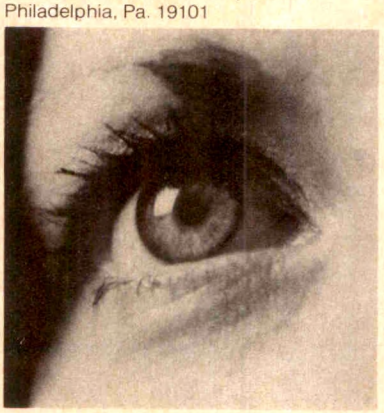
'Stoxil' Ophthalmic Solution should not be mixed with other medications.

Adverse Reactions: Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally, corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

How Supplied: 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

Stability: The Solution should be stored in refrigerator until dispensed. 'Stoxil' Ophthalmic Ointment does not require refrigeration.

Smith Kline & French Laboratories
Division of SmithKline Corporation
Philadelphia, Pa. 19101



Specific

Stoxil®

brand of
idoxuridine

works against Herpes Simplex Keratitis

Two dosage forms for patient convenience

Ointment 0.5%
(applications q4h and h.s.)

Solution 0.1%
(applications hourly and every 2 hours at night)



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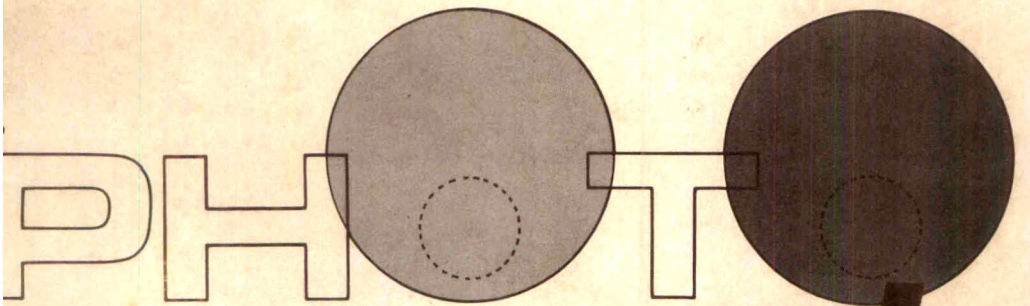
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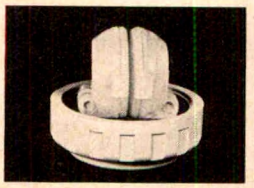
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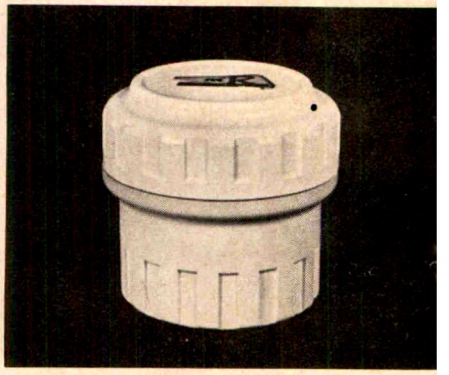
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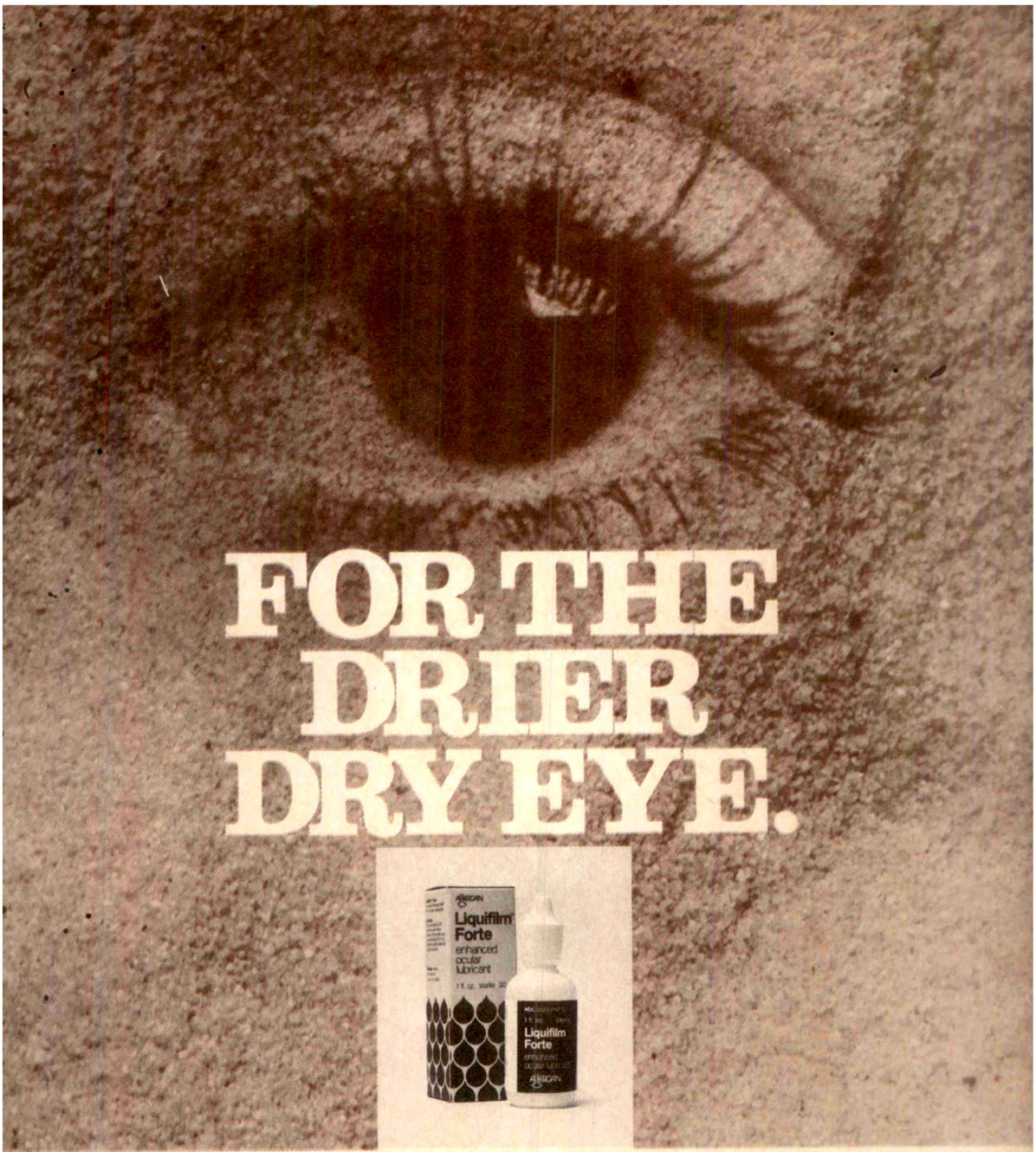
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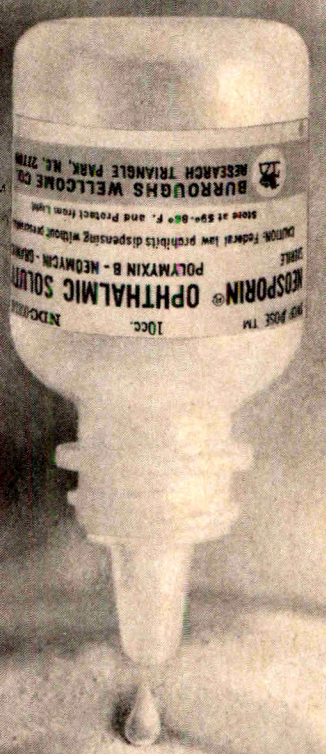
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WARNINGS:
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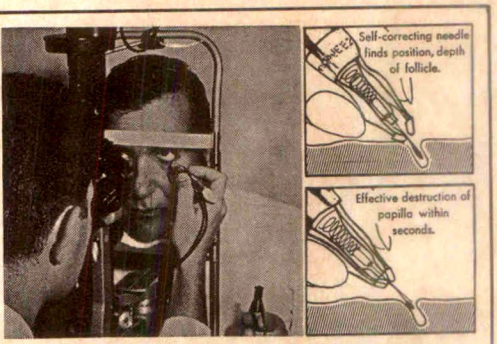
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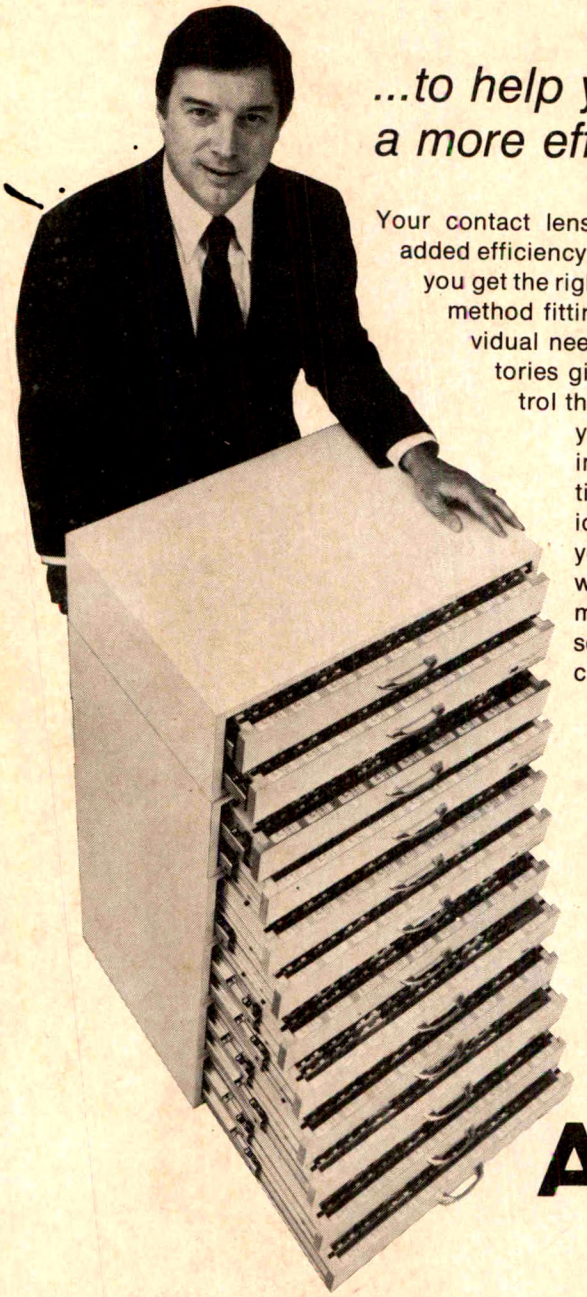
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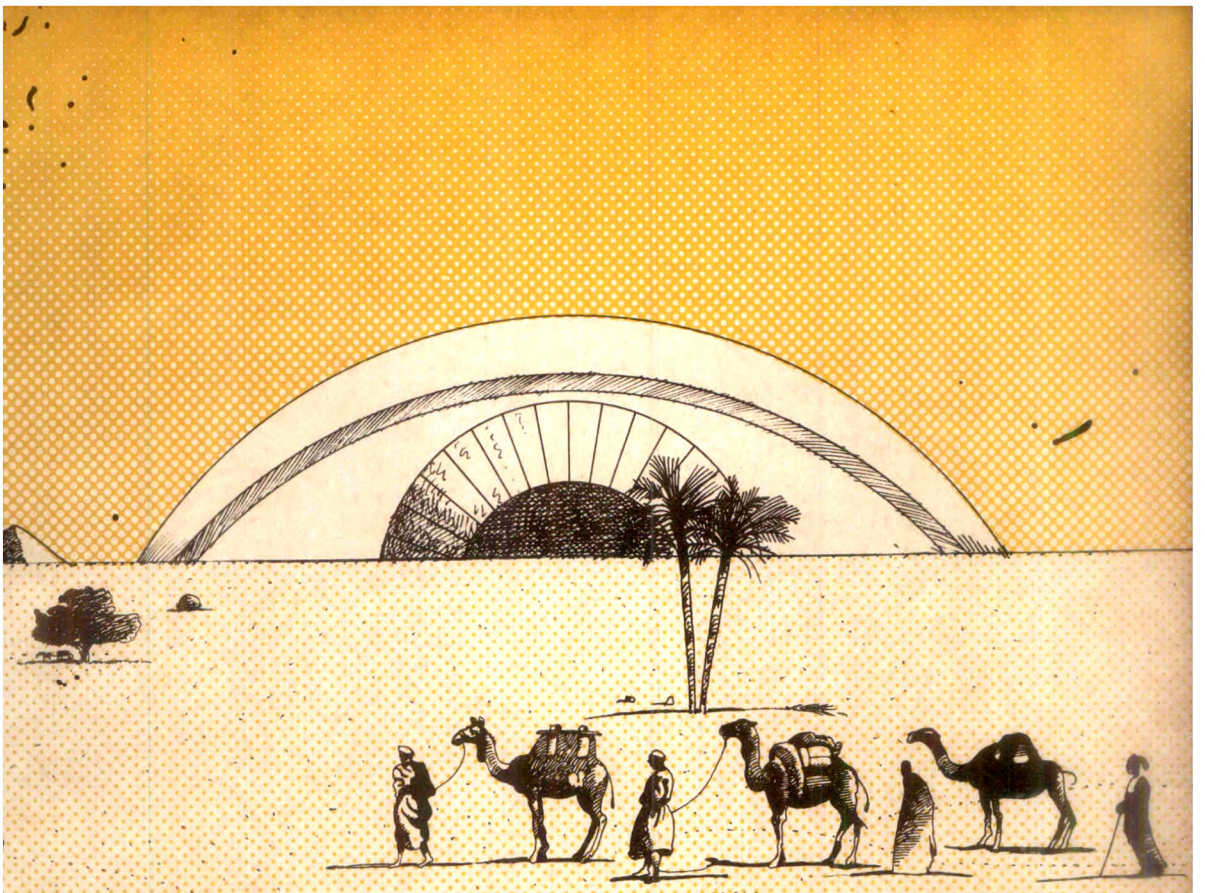
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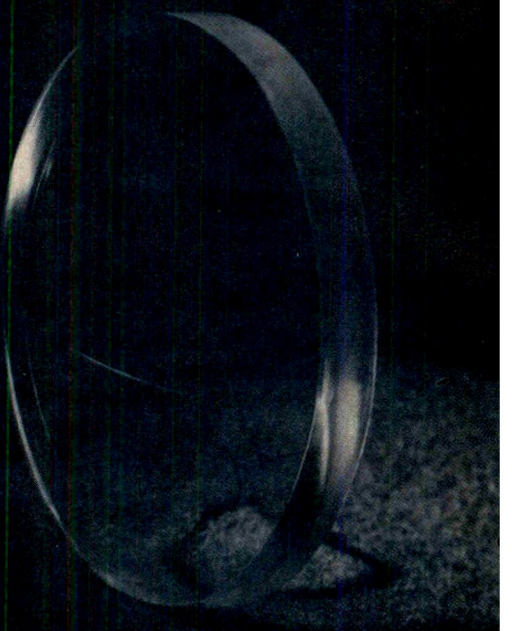
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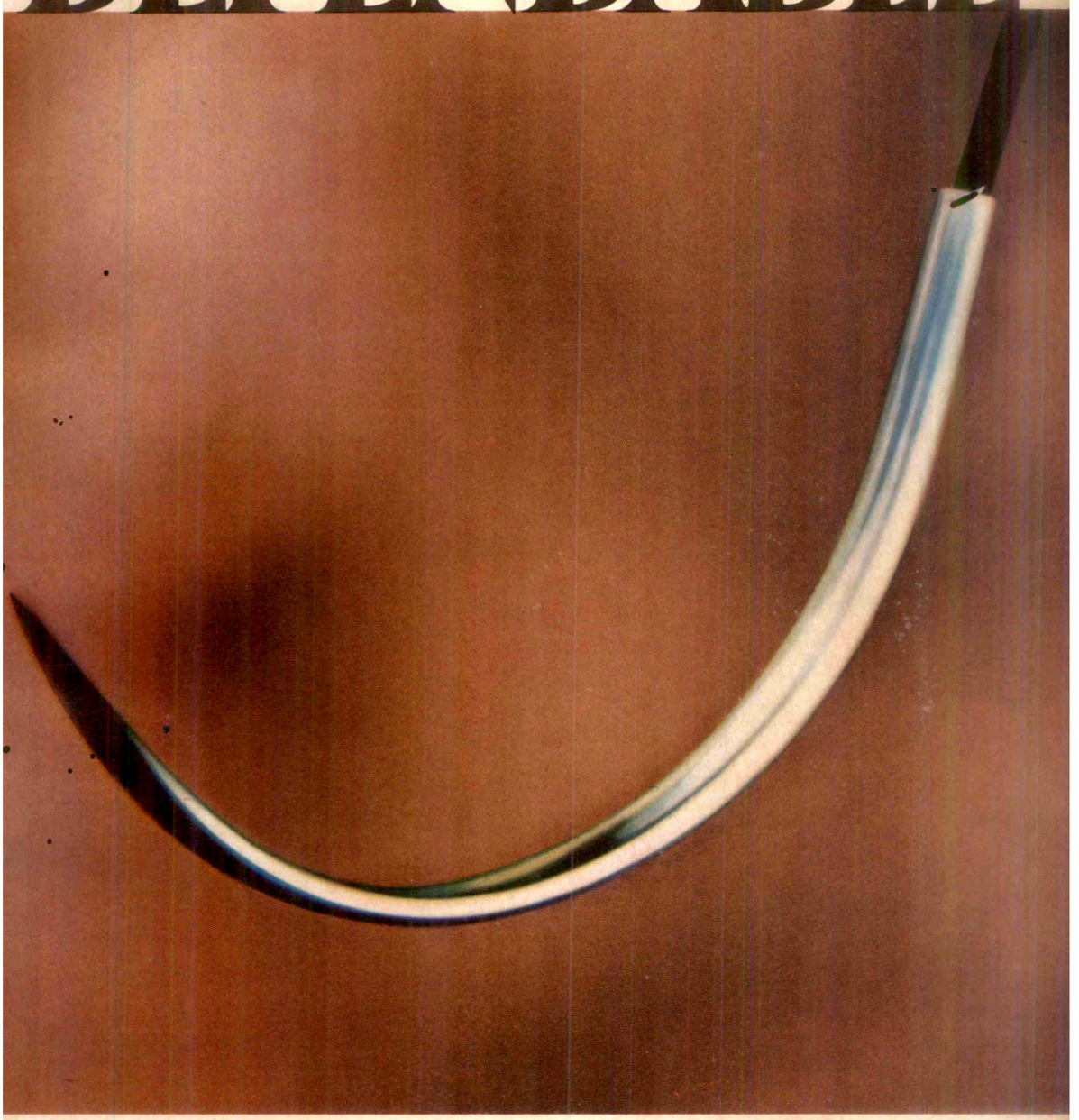
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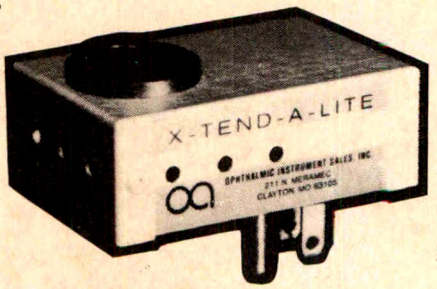
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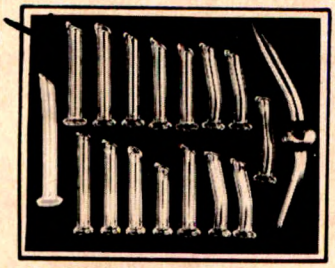
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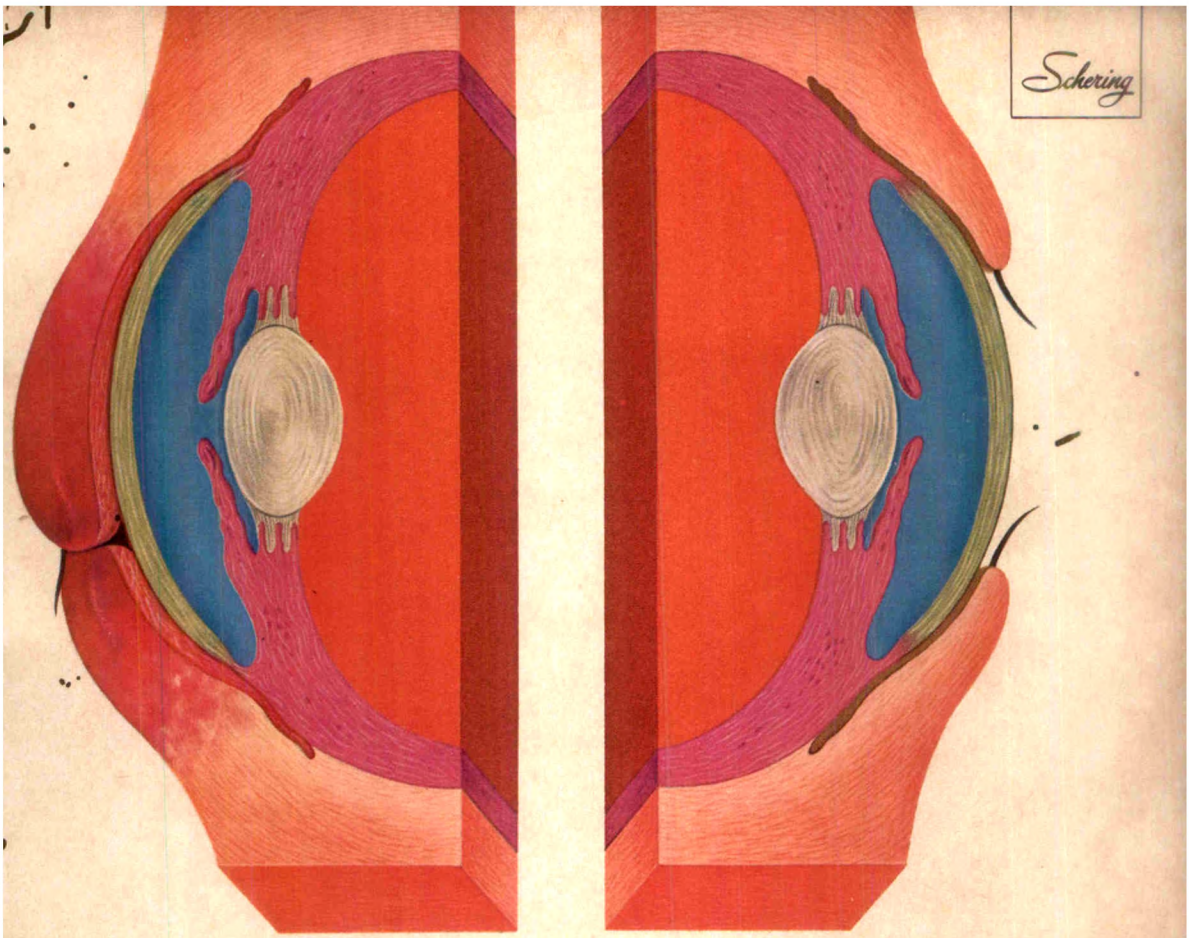
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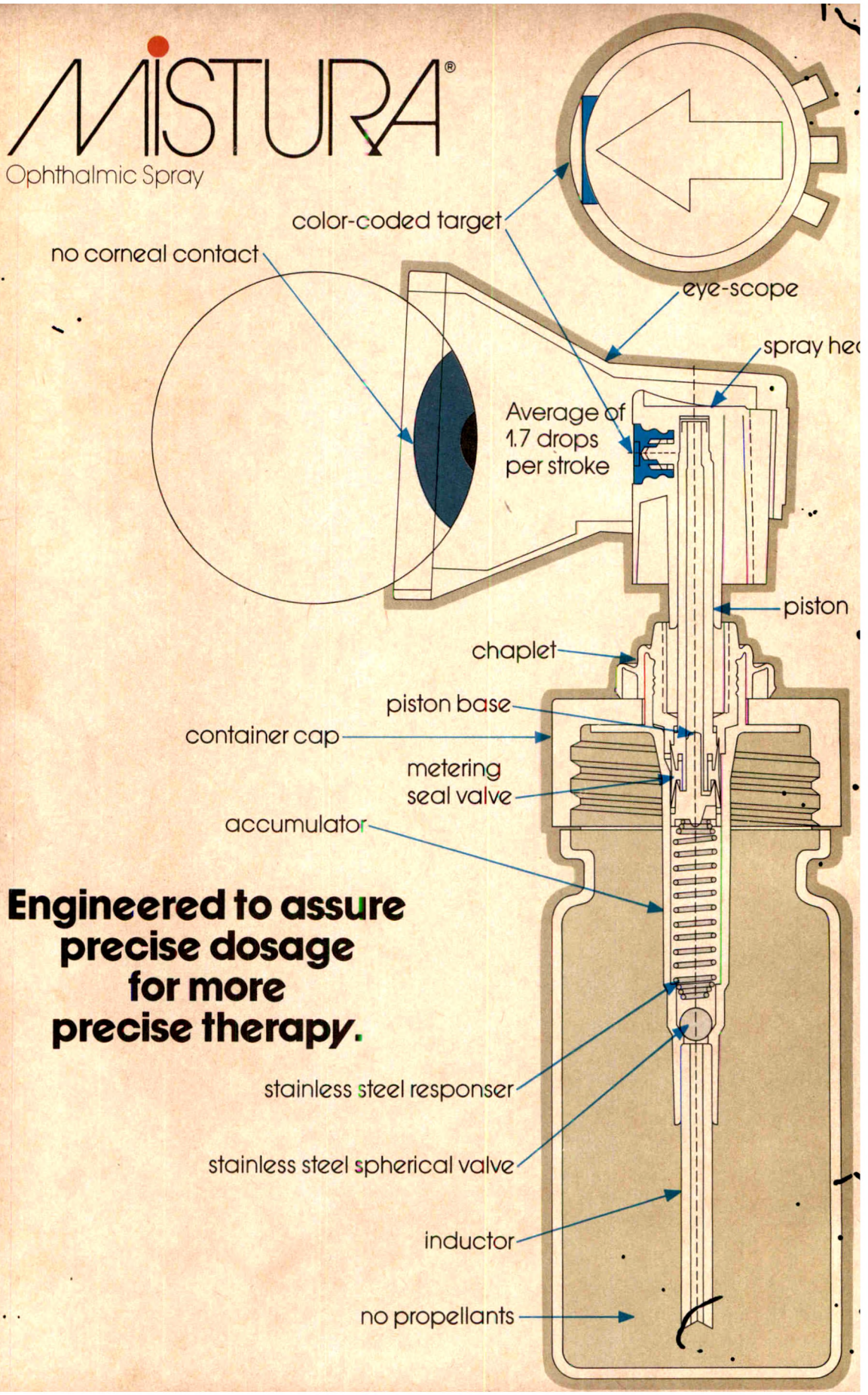
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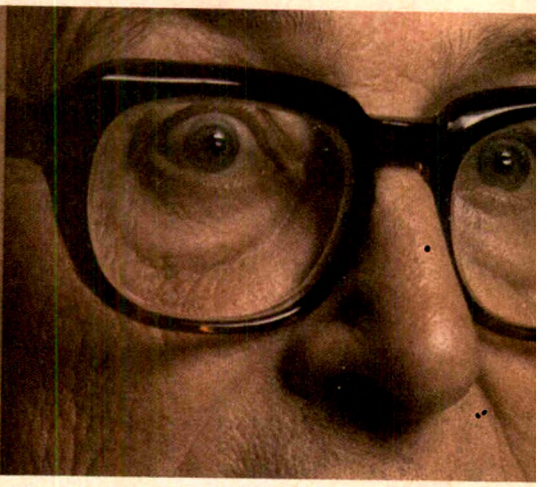
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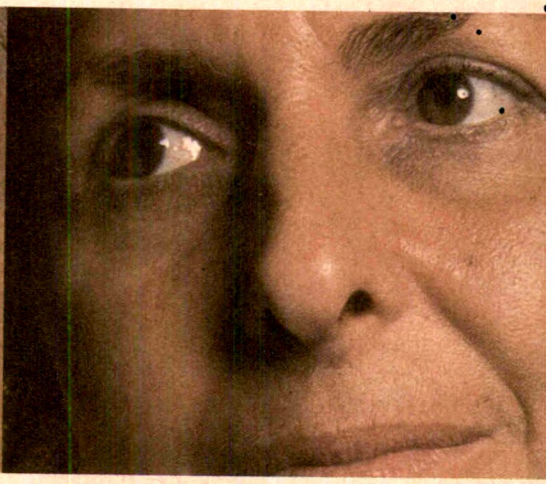
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- Handsome streamlined design
- Can be used anywhere
- No need for awkward positions
- Fast coverage

I can use a dropper—with some difficulty

- Easy to self-apply at home or away
- No aiming, no wasted medication
- No mirror needed
- Held against orbit to assure steadiness
- Engineered to promote dosage adherence
- A wide safety zone to prevent injury
- No need for patient to bend his head back





I can't use a dropper at all

- "Straightforward" delivery—eliminates the need for patient to bend his head back
- Even tremor patients can apply
- No thin tapered end to cause global injury
- No eye contact with medication outlet
- Gentler than a drop, faster than a blink

I've never used a dropper

- Designed to avoid "dropper phobia"
- No experience needed
- No practice needed—patient instructions make i as easy to use as pressing a button
- No blink reaction to waste dosage
- Engineered for safety
- Designed for immediate patient acceptance
- Consistent accuracy—average of 1.7 drops per application

MISTURA®

Ophthalmic Spray

MISTURA® D Phenylephrine HCl 0.12% Ophthalmic Solution Sterile

Description: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.

Contains: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.

Directions: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.
When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.

Caution: Should not be used in the presence of narrow-angle glaucoma.

Warning: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

How supplied: Available in sterile 15 ml. mist dispensing bottles.

MISTURA® D.Zn Phenylephrine with Zinc Sulfate Ophthalmic Solution Sterile

Description: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.

Actions: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.

Indications: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.

Contraindications: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.

Warnings: If irritation persists or increases, discontinue use and consult a physician.

Dosage and administration: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.
When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

How supplied: Available in sterile 15 ml. mist dispensing bottles.

MISTURA® C Carbachol Ophthalmic Solution Sterile

Contains: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.

Actions: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.

Indications: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.

Contraindications: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.

Precautions: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.

Dosage and administration: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.
When used according to the accompanying directions for use, each application delivers 1.7 drops of MISTURA C.

How supplied: Available in sterile 15 ml. mist dispensing bottles.

MISTURA® E l-epinephrine Ophthalmic Solution Sterile

Description: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with: benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.

Actions: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.) MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)

Indications: Chronic simple glaucoma.

Contraindications: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.

Warnings: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].

Precautions: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.
Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.

Dosage and administration: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.
When used according to the accompanying directions for use, each application delivers 1.7 drops of MISTURA E.
NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.

How supplied: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES

1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968

MISTURA® P Pilocarpine Hydrochloride Ophthalmic Solution Sterile

Contains: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 as a preservative sodium acetate, disodium edetate, sodium chloride, and purified water.

Indications: MISTURA P *pilocarpine HCl* is indicated for:
1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

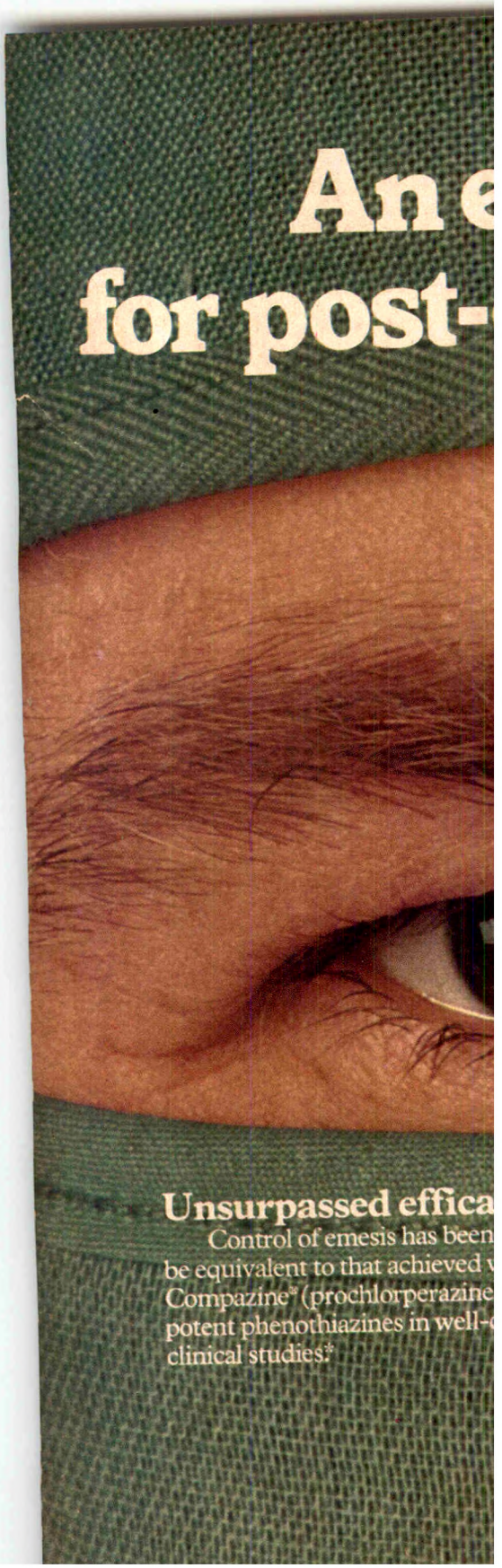
Precaution: Undesirable side reactions to MISTURA P are rare; however, on prolonged use, classic mucosal sensitization to pilocarpine may occur.

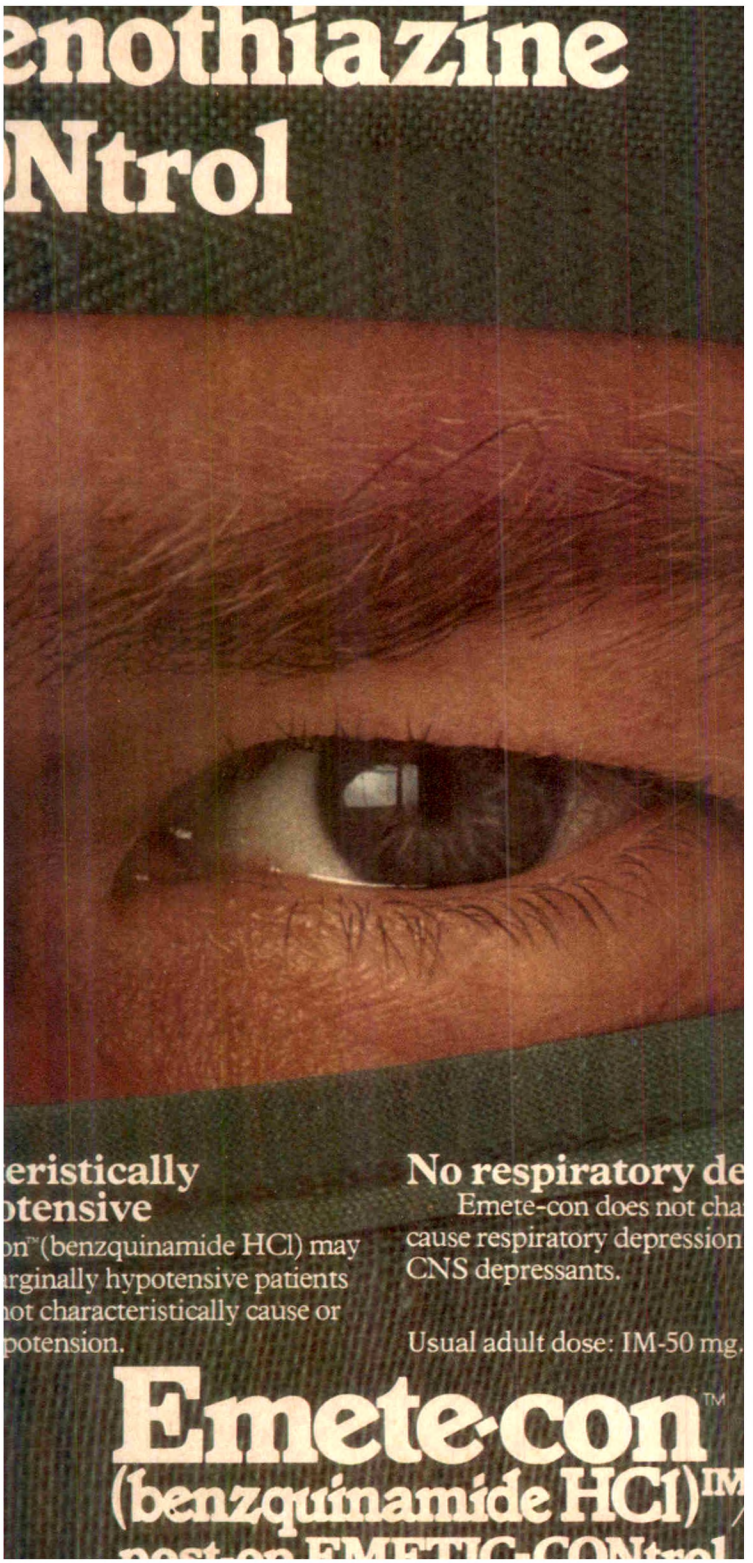
Dosage and administration:
1. For glaucoma, the recommended dosage is 1 mist application two to four times a day of the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations should be used.
3. The dosage and strength required to reverse mydriasis depends on the cycloplegic used.
When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA P.

How supplied: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles.

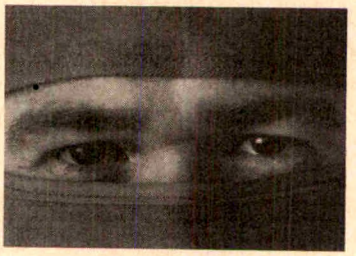
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rginally hypotensive patients
ot characteristically cause or
potension.
No respiratory de
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cause respiratory depression
CNS depressants.
Usual adult dose: IM-50 mg.
Emete-con™
(benzquinamide HCl) IM

Emete-con™
(benzquinamide HCl) IM/IV
post-op EMETIC-CONtrol



PRESCRIBING INFORMATION
Emete-con™ (benzquinamide hydrochloride)
For Intramuscular and Intravenous Use

Description. Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide hydrochloride) is N, N-diethyl-1,3,4,6,7, 11b-hexahydro-2-hydroxy-9, 10-dimethoxy-2H-benzo [a] quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5$. HCl and the molecular weight is 441.

Emete-con for injection contains benzquinamide hydrochloride equivalent to 50 mg/vial of benzquinamide and 0.45 mg/vial of citric acid. When reconstituted with 2.2 ml of proper diluent, each vial yields 2 ml of a solution containing benzquinamide hydrochloride equivalent to 25 mg/ml of benzquinamide and 0.02% citric acid. When reconstituted this product maintains its potency for 14 days at room temperature.

Actions. Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con (benzquinamide hydrochloride) should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected—*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg—1.0 mg/kg))

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con (l
quinamide hydrochloride) should be injected
within the mass of a larger muscle. The de
area should be used only if well developed
jections should not be made into the lower and
thirds of the upper arm. Aspiration of the sy
should be carried out to avoid inadvertent i
vascular injection.

Therapeutic blood levels and demonstrable
emetic activity appear within fifteen minut
intramuscular administration. When the obje
of therapy is the prevention of nausea and v
ing, intramuscular administration is recomme
at least fifteen minutes prior to emergence
anesthesia.

Intravenous: 25 mg (0.2 mg/kg—0.4 mg/k
a single dose) administered slowly (1 ml pe
to 1 minute). Subsequent doses should be
intramuscularly.

The intravenous route of administration sh
be restricted to patients without cardiovas
disease (See WARNINGS). If it is necessar
use Emete-con intravenously in elderly or de
tated patients, benzquinamide should be adm
tered cautiously and the lower dose rang
recommended.

This preparation must be initially reconstit
with 2.2 ml of Sterile Water for Injection,
teriostatic Water for Injection with benzyl alc
or with methylparaben and propylparaben.
procedure yields 2 ml of a solution equivale
25 mg benzquinamide/ml. which maintain
potency for 14 days at room temperature.

Overdosage. *Manifestations:* On the basis of a
animal toxicology studies, gross Emete-con
dosage in humans might be expected to man
itself as a combination of Central Nervous Sy
stimulant and depressant effects. This specula
is derived from experimental studies in w
intravenous doses of benzquinamide, at least
times the human therapeutic dose, were adm
tered to dogs.

Treatment: There is no specific antidote
Emete-con overdosage. General supportive
sures should be instituted, as indicated. Atro
may be helpful. Although there has been no di
experience with dialysis, it is not likely to b
value, since benzquinamide is extensively bo
to plasma protein.

How Supplied. Emete-con for IM/IV use is a
able in a vial containing benzquinamide
equivalent to 50 mg of benzquinamide in packa
of 10 vials.

Caution. Federal law prohibits dispensing with
prescription.

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New York, New York 10017

Bibliography

Zauder, H. L., et al.: Prophylaxis of Postoperative Emesis, Scientific Exhibit presented at 122nd Annual Convention of the A.M.A., June 23-27, 1973.

Lutz, H., and Immich, H.: Antiemetic effect of benzquinamide in postoperative vomiting. Curr. Ther. Res. 14:178, April, 1972.

Finn, H., et. al.: Antiemetic efficacy of benzquinamide. N.Y. J. Med. 71:61, March 15, 1971. Larrauri, R. M.: Benzquinamide parenteral for the treatment of post-operative nausea and vomiting. Curr. Ther. Res. 11:65, March, 1969.

Steen, S. N. and Yates, M.: The Effects of Benzquinamide and Prochlorperazine, Separately and Combined, on the Human Respiratory Center. Anesthesiology 36:519, May, 1972.

Emete-con™
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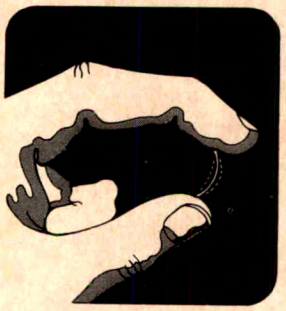
Each vial contains benzquinamide hydrochloride equivalent to 50 mg. of benzquinamide with 0.45 mg. of citric acid.

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II. The Oxford Congress (held in July, published in the Winter)

III. The Cambridge Symposium on *'The Eye in Connective Tissue Disease'* (held in September, published in the following Spring)

IV. Papers from the Irish, Scottish and provincial societies, Reports from affiliated organizations throughout the world, and the Annual Index (published in the Summer)

The first part of the volume was published Autumn 1974

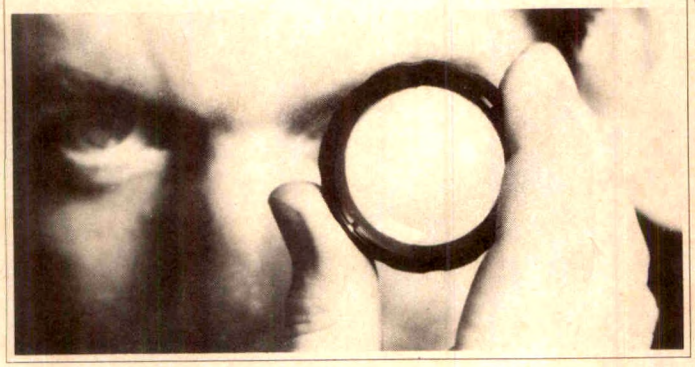
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Corresponding Secretary
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Executive Secretary

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The manuscript should be arranged in the following order:

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3. Acknowledgments
4. References
5. Tables
6. Legends for figures

Each major section should begin on a separate sheet.

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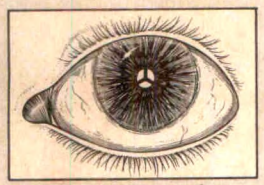
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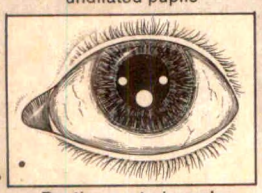
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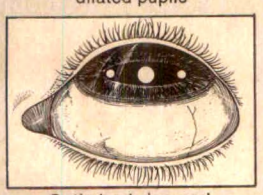
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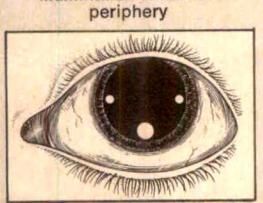
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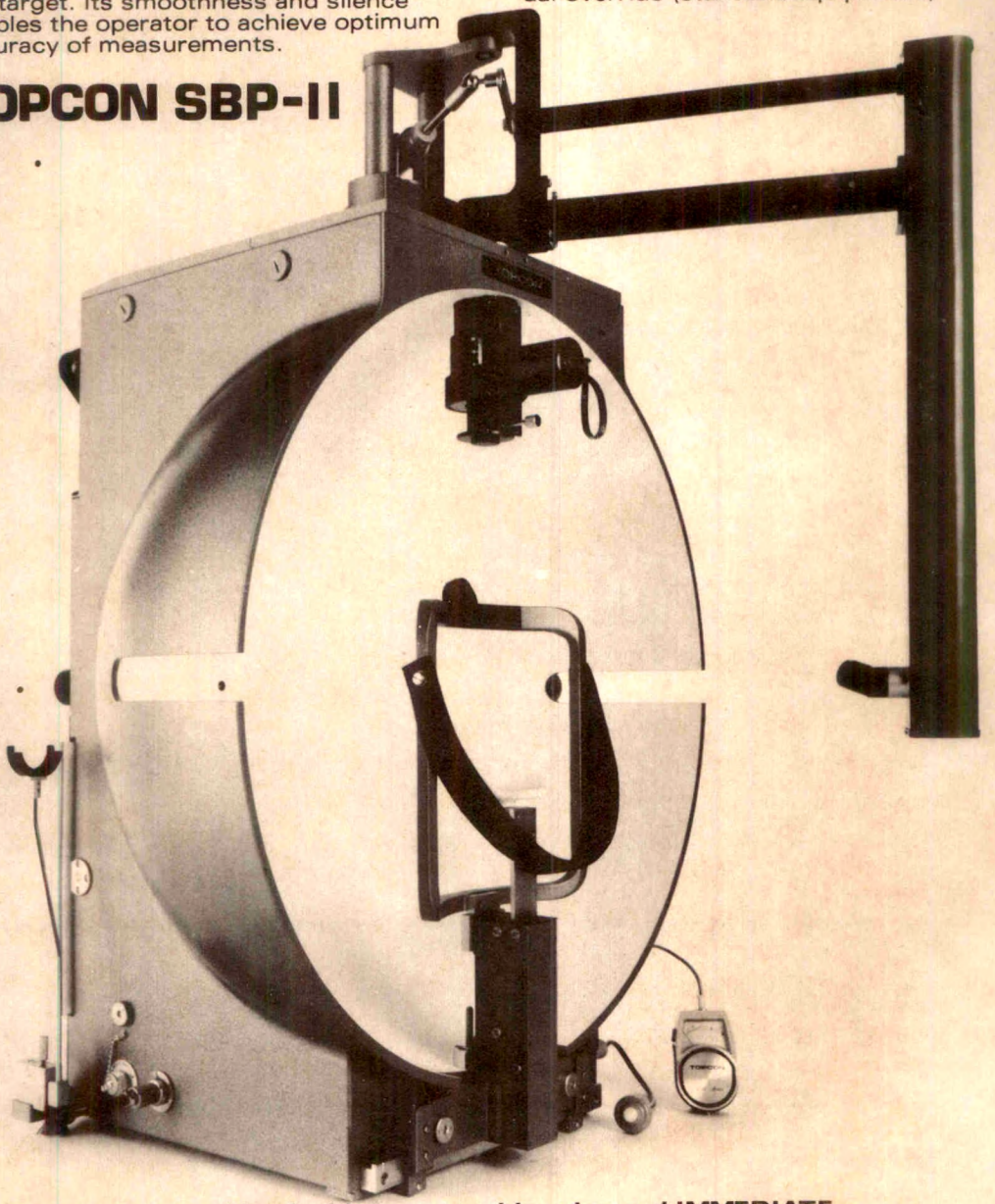
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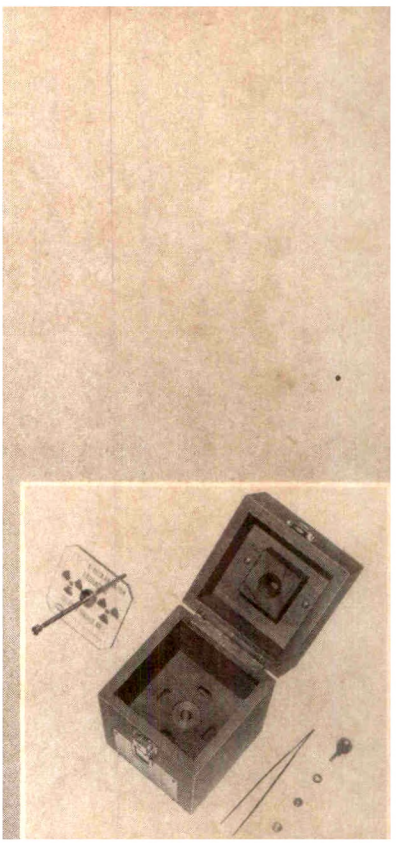
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Notes of a Biology-Watcher

ON ETYMONS AND HYBRIDS

An etymon is supposed to be a pure ore of a word, crystalline, absolutely original, signifying just what it was always intended to signify. They are very rare these days. Most of the words we use are hybrids, pieced together out of old, used speech by a process rather like the recycling of waste. We keep stores of discarded words around, out beyond the suburbs of our minds, stacked like scrap metal.

When you do run across a primary, original word, the experience is both disturbing and vaguely pleasurable, like coming across a friend's picture in an old high-school annual. They are all very old, and the most meaningful ones date all the way back to Indo-European roots,[1] which became the parents of cognate words in Sanskrit, Persian, Greek, Latin and, much later, most of the English language. *Sen* meant old, *spreg* meant speak, *swem* was swim, *nomen* was name, a *porko* was a young pig, *dent* was a tooth. *Eg* was I and my ego, *tu* was thou, *yu* were you, and *me* was me. *Nek* was death. A *mormor* was a murmur. *Mater, pater, bhrater* and *swesor* were the immediate family, and *nepots* were the nephews and nieces. A *yero* was a year. A *wopsa* was a wasp and an *apsa* was an aspen. A *deru* was a tree, and also something durable and true. To *gno* was to know. *Akwa* was water, and to *bhreu* was to boil. Using basic Indo-European and waving your hands, you could get around the world almost as well as with New York English.

Some of the first words have changed their meaning drastically, of course. *Bhedh* was the source of our bead, but it originally meant to ask or bid; bead started out as a word for prayer. *Dheye* meant to look and see, and moved from *dhyana* in Sanskrit, meaning to meditate, to *jhana* in Pali, to *ch'an* in Chinese, to *zen* in Japanese.

You'd think modern science would be inventing lots of brand-new etymons to meet its needs, but it is not so. Most of our terms for new things are reconditioned words. Thermodynamics, first spoken a century ago, is an antique shop: the I.E. *gwher,* meaning warm, was turned into *thermos* in Greek, while *deu,* to do, became *dunesthai* in Greek, meaning capable of, and hence dynamic (the same *deu* is the source of dynamite, bonus and bonbon). A "bit," in computer jargon, although designed as the least ambiguous of terms by combining parts of "binary" and "digit," has a tangle of meanings in its origin: binary came from *dwo,* meaning two, which led also to twig, double and doubt; digit began as *deik,* to show or teach, and moved into English in company with token, paradigm and ditto, also toe.

A nucleic acid (from *ken,* later *knu,* plus *ak*) is a sort of nut coupled to something sharp.

Cholera toxin could be translated by an outsider, new to our language, as a bright and shiny bow and arrow. *Ghel* was at first the word for shining, later yellow; it turned to *ghola,* then *khole* in Greek, meaning bile, then into choler and cholera in English. Toxin was originally *tekw,* a word meaning to run or flee, later becoming *toxsa* in Persian and *toxon* in Greek, meaning bow and arrow; the toxin meaning may have come from the poison used to tip the arrows, or, as Robert Graves suggested, from the yew tree *taxus* from which arrows were best made and whose berries were long thought to be poisonous.

The word for poison came by a devious route, like a long delayed afterthought. It derives from *poi,* to drink, becoming *potare* in Latin, whence potion (and also symposium, from *sun,* together, plus *posis,* to drink). The venomous meaning did not come until the notion of love-potions evolved, and then the idea of poison came to consciousness.

There is the same strange history behind the word venom. This began as the simple word *wen,* meaning to wish or will, leading more or less directly to win. Along the way, a fork led to venus, venery and venerate, all indicating varieties of love. The love-potion was called *venin,* and somehow

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this gradually acquired today's sense of venom.

Nobody can explain why poison and venom come from love-potions. Perhaps it was because the pharmacology of the day was primitive and chancy, a very thin line away from toxicology. Or maybe there was a commonsense consensus that any sort of chemical additive intended to induce false love is, but its nature, a fundamental poison. It tells something important about the good taste of earlier human beings that venom and poison were taken resentfully out of the hands of artificial lovers and transferred to the stings of insects and the fangs of serpents.

A virus is a very ancient word, despite the newness of its meaning to us. The root was *weis*, meaning to flow, in the sense of oozing, and it went first from *wase* in Old English to *wose* in Middle English and thence to ooze itself. The meaning of something twisty and slippery derived, and the weasel was named. The associations became more unpleasant, indicating something noxious, and virulence and viruses were the resulting words. Noxious, incidentally, came from *nek*, meaning death, by way of *necare* and *nocere* in Latin, providing necropsy and cognate words for us; nectar was the drink of the gods because it prevented death (*tar* meaning to overcome).

All of this has the sound of a series of accidents. It may be that the evolution of language was largely a matter of luck, like the evolution of creatures. Even though the facts of the matter have been firmly nailed down by two centuries of meticulous philological scholarship, there is a general, unavoidable sense of high improbability in the whole business. If this is the way words evolved, it seems to have depended upon a lot of pure chance, or, as the French say, hazard.

Chance. Now there's a word. Partridge[2] gives it almost two columns of the finest print, but not under itself. If you want to look up chance you must find cadence, the nearest thing to an etymon but a long way off at that. Cadence comes from *kad*, meaning to fall. Kad led to *cadere* in Latin and *cad* in Sanskrit, also meaning to fall, sometimes to die, and from this came a cascade of words with the sense of risk and transiency: cadaver, decay, casualty, deciduous and casuistry.

The notion of falling gave rise to words like cadence and cadenza, and cascade. The idea of chance came, as you may have guessed, from the falling of dice.

Incidentally, hazard also came from dice, by way of Old French *hasard* and Spanish *azar*, from the Arabic *yasara*, to play at dice. The game of dice is named for the die used for playing, and this comes from I.E. *do*, which originally meant to give, later changing to donation, dowry, endow, dose and antidote. In vulgar Latin the verb *dare* came to mean play, leading to *datum* as a playing piece, then *dee* in Old English, then die and dice.

It is obvious that this sort of thing could not have been worked out by any intentional human intelligence. Today's language is the result of an interminable series of small blunders, one after another, leading us back through a near infinity of time. The words are simply let loose by all of us, allowed to fly around out there in the dark, bumping into each other, mating in crazy ways, producing wild, random hybrids, beyond the control of reason.

Just think how much better we could manage if we put our minds to it. All it needs is better, clear-headed organization, with a more efficient administrative control of human speech. Management is what has been lacking. If, as seems to be the case, sometimes deplorably, today's most necessary words have been created by this improbable process of hybridization, then hybridization is the business we should now begin to take in hand. All we have to learn is how to pair one word with another so that mating can occur, and then sort out the progeny to our liking. Governments will need to become involved in this, for we shall be requiring whole new institutions all around the earth, occupying huge tracts of land in national capitals, devoted to the breeding of words, like the agricultural experimental stations of the past century. The breeding of words can become the bureaucratic preoccupation for the future, as in the past, but better organized, with more committees. Given a new in-house capability for the generation of novel words, substituting

numbers for the input of letters wherever feasible, and fiscally optimized by computer creativity for targeting on the core issues relating to aims, goals and priorities, we might at last be freed from our dependence on the past. New hybrids, synthesized by management skills in agencies of our local institutions, could then take the place of those Indo-European words, with all their primitive, precivilized, embarrassing resonances.

To start with, we ought to get another word to take the place of hybrid. Not that it doesn't describe itself satisfactorily, but there is something not sufficiently straightforward about it for the scientific needs it is intended to serve. Hybrid is itself a relatively new word, easily disposed of without sentiment, but standing blank-faced behind it is the Latin *hybrida,* which was the name for the unsuitable offspring of a wild boar and a domestic sow. The word had no use in English until around the 17th century, when a casual mention of hybrids was made, referring to the boar-sow mismatch. It was not until the mid 19th century that it really entered the language. At that time it was needed for botany, zoology, and the rapidly developing discipline of philology, and there were even usages in politics (hybrid bills in parliament).

The real trouble with hybrid is in its more distant origins. It is a word that carries its own disapproval inside. Before being hybrid it was *hubris,* an earlier Greek word indicating arrogance, insolence against the gods. Hubris itself came from two I.E. roots, *ud,* meaning up or out, and *gwer,* with the meaning of violence and strength. Outrage was the general sense. Hubris became a naturalized English word in the late 19th century, exhumed by classical scholars at Oxford and Cambridge and promptly employed as slang to describe the deliberate use of high intellectual capacity to get oneself into trouble. Hubris was the risk of losing in an academic equivalent of jiu-jitsu; if you used your full mental powers you could be hurled, by your own efforts, out into limbo.

The latest hybrids to join the products of botanists and zoologists are the viruses, and some of these we are now manufacturing ourselves, making them up and then breeding them. It has recently been announced that we can construct hybrids of viral and bacterial DNA, chains of genetic information capable of going either way. There is nothing to prevent us from linking nucleic acids from mammalian cells to any number of viruses, oncogenic or otherwise, as easily as stringing beads. Nobody has any idea what the biologic properties of these new creatures will turn out to be. The latest comment on this line of work is a letter in *Science,*[3] addressed to the National Academy of Sciences, pointing out that the potential risks to human and other animal and plant life posed by these invented agents are beyond present calculation, and now it is rumored that the work on such things has, for a time anyway, been brought to a stop. These are hybrids earning their name.

Make up our own language? With committees? In institutes? What a way to talk.

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LEWIS THOMAS, M.D.
N. Engl. J. Med. 290:1069, 1974

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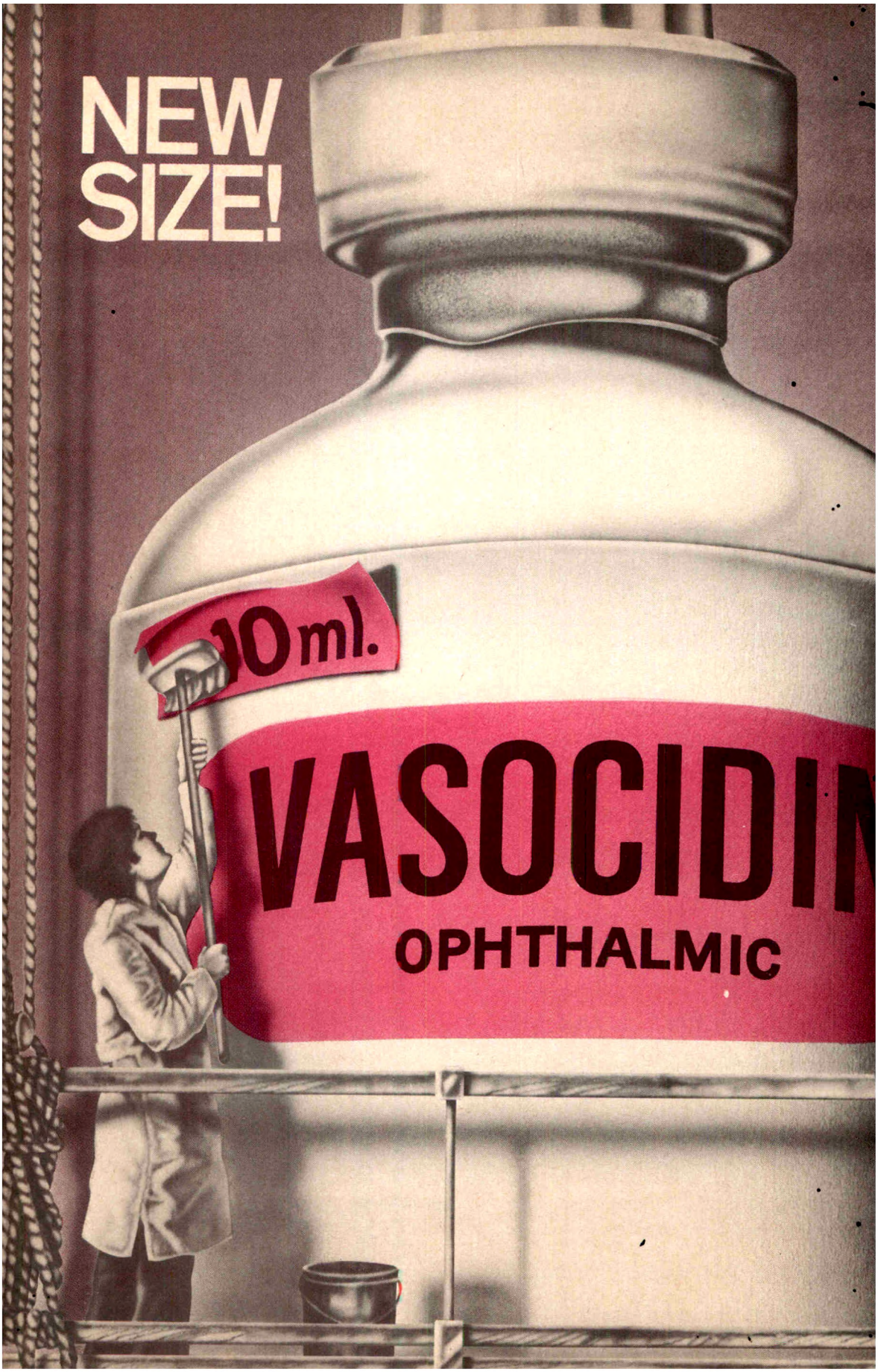
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1. Haas, J. S. and Merrill, D. L.: Amer. J. Ophthal. 54:21, 1962. **2.** Linn, M. L. and Jones, L. T.: Amer. J. Ophthal. 65:76, 1968.

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 80 JULY, 1975 NUMBER 1

PIGMENT EPITHELIUM PROLIFERATION IN RETINAL DETACHMENT (MASSIVE PERIRETINAL PROLIFERATION)

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After retinal detachment is created in owl monkeys, some eyes develop a great similarity to what is clinically termed "massive vitreous retraction" (MVR) or "massive preretinal retraction" (MPR),[1] thus providing a unique opportunity to study this disease in an experimental model. In this model proliferations on and under the retina, in the vitreous cavity, and at the ora serrata play a major role in the development of this complication.

The purpose of the present study is to examine histologically and electron microscopically the role of pigment epithelial cells. There are three cell types derived from the pigment epithelium which proliferate inside the eye and play a critical role in this disease.

Subsequent papers will present the properties of retinal pigment epithelium,[2,3] the role of glial cell proliferation,[4] and clinicopathologic correlation. These observations finally lead to a reevaluation and new understanding of this disease. We propose to call this disease "massive periretinal proliferation" (MPP).

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Presented in part before the Association for Research in Vision and Ophthalmology Annual Spring Meeting, Sarasota, Florida, April 25-29, 1974, and the Ninth Meeting of the Club Jules Gonin, La Baule, France, May 12-18, 1974.

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MATERIALS AND METHODS

Retinal detachments were produced in owl monkey eyes[1] by injection of five units of hyaluronidase into the vitreous cavity with mechanical destruction of the vitreous tissue by repeated aspiration and reinjection through a hypodermic needle and final quick injection of the aspirate against the retina to create a retinal hole and a surrounding detachment. The detachments increased spontaneously over the following weeks and in most eyes total retinal detachments developed between the second and the fourth week.

The eyes were observed from one hour to 27 months after production of the retinal detachment (Table 1). On the day of enucleation the eyes were examined ophthalmoscopically with the slit-lamp by using the Goldmann 3-mirror contact lens; fundus photographs were taken.

For histologic evaluation, the eyes were fixed in a modified Kolmer fixative[5] for 24 hours. To preserve the shapes of the eyes approximately 0.1 ml of the fixative was injected into the anterior chambers. After one day of fixation the corneas were removed with a trephine to avoid deformation of the globes during dehydration and to allow embedding material easy access to the inner eye. After dehydration, the globes were embedded in paraffin. Vertical sections 5 μ thick

TABLE 1

SURVEY OF EXAMINED EYES

Duration of Retinal Detachment		No. of Eyes	Eyes Used for Autoradiography	Eyes With Pigment Epithelial Proliferation* Proven by	
				Light Microscopy	Electron Microscopy
Hr	1	6			
	6	2			
	12	2			
	18	2			
Day	1	13	6		
	3	6	4		
Wk	1	9	6	2	
	2	6	2	4	
	3	2			
	4	26	14	17	5
	5	6	3	3	
	6	1		1	
	8	6	3	6	
	9	17	16	15	7
	10	7	4	5	
	12	6		3	
	14	2		2	
	16	2	2	1	
	17	2	2	2	
	18	1		1	
Mo	5	2		2	
	6	1			
	8	2		2	2
	11	2		2	
	27	1	1	1	
Total		132	63	69	14

* Including proliferation at ora serrata but excluding proliferation of macrophages.

were made in five areas: (1) through the temporally located retinal hole; (2) through the macular area; (3) through the disk; (4) and (5) through nasal parts of the eye at distances from the disk corresponding to those of areas 1 and 2. All histologic sections were stained with hematoxylin-eosin and PAS. Selected sections were stained for detection of collagen (Mallory).

For electron microscopic purposes, 0.1 to 0.2 ml of 6% buffered glutaraldehyde was injected into the vitreous cavity immediately before enucleation. The whole enucleated eye was then fixed in glutaraldehyde and opened circumferentially anterior to the ora serrata. Specimens were photographed, then excised and postfixed in 2% phosphate-buffered osmium tetroxide, dehydrated in a graded series of ethanol, and embedded in Epon. For histologic evaluation 1.5-μ sections were stained with paraphenylenediamine. Thin sections (0.05 μ) were stained with uranyl acetate and lead citrate and were examined under a JEM-7 electron microscope.

To study the proliferative activity inside the eye we injected some eyes intravitreally with 0.1 ml of tritiated thymidine two hours before enucleation (50 μCi thymidine methyl-H-3, specific activity 5.0 curie/mM). Sections were coated with Kodak nuclear track emulsion NTB2, exposed for five days, and

developed in Kodak D19, and then stained with hematoxylin.

(Autoradiography after thymidine-H-3 incorporation demonstrates DNA synthesis. The radioactive label of cells is usually an indication for subsequent mitosis of a cell. Since the DNA synthesis time is much longer than the mitosis time, this technique allows one to detect multiplication far better than observation of mitosis.)

Results

First cell type: pigment epithelial macrophages—In the subretinal space, directly underlying the retina or embedded between outer segments, preretinally and intravitreally, cells were encountered that usually appeared singly or in clusters. The cells were large but of varying size, usually round or oval. The large round-to-oval nucleus was often eccentrically located. The cytoplasm often contained an abundance of wedge-shaped or round pigment granules, but there were also cells containing little or no pigment. The cytoplasm, when not hidden by pigment granules, was often filled with granular material (Fig. 1).

When these cells were embedded between the outer and inner segments of the retina their cytoplasm seemed to have many processes, and, therefore, these cells had irregular shapes. The nuclei also were commonly irregular in shape. Pigmentation of these cells varied greatly and granules were either wedge-shaped or round.

Electron microscopy of these cells showed a cell with much cytoplasm and a relatively large nucleus, usually located marginally. The cytoplasm contained free or enveloped electron-dense, round, or wedge-shaped pigment granules. Some of them seemed to be within phagosomes. When the cells were located under the retina, the phagosomes also contained lamellar inclusion bodies (Fig. 2) that were phagocytosed outer segment material. When the cells were found in the vitreous cavity they contained other debris, including erythrocytes. The cell surface had many microvilli. The microvilli were found in contact with neighboring cells when the

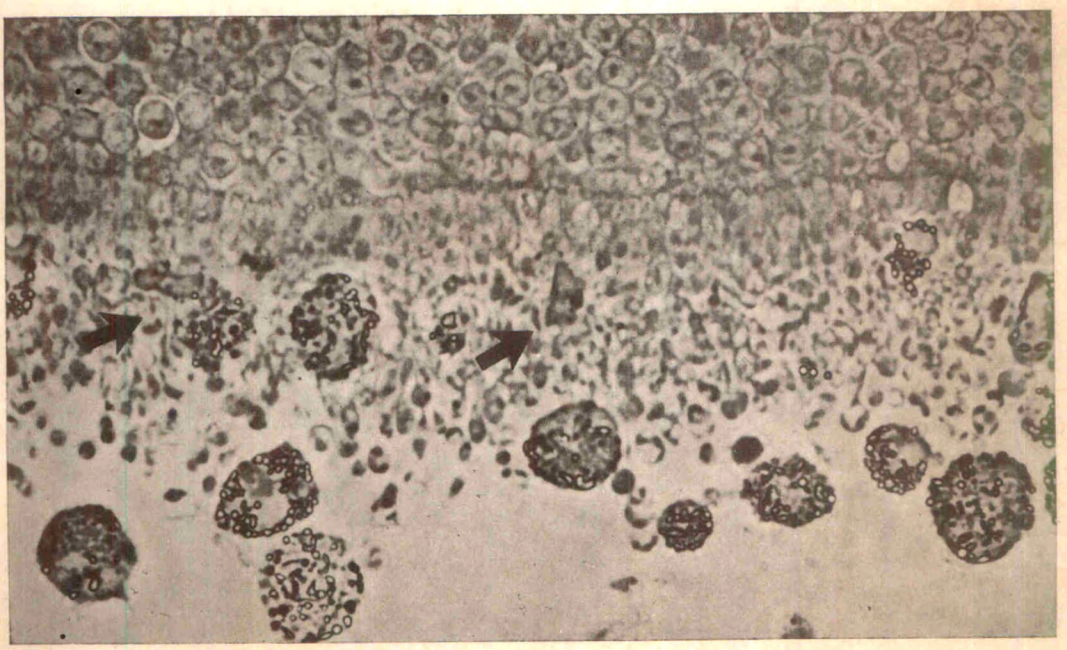


Fig. 1 (Machemer and Laqua). Large round cells, usually pigmented and with granular material in the cytoplasm are found under detached retina. When in the outer segment layer, the cells may have irregular shapes (arrows); 1-μ thick section, 4-week-old retinal detachment.

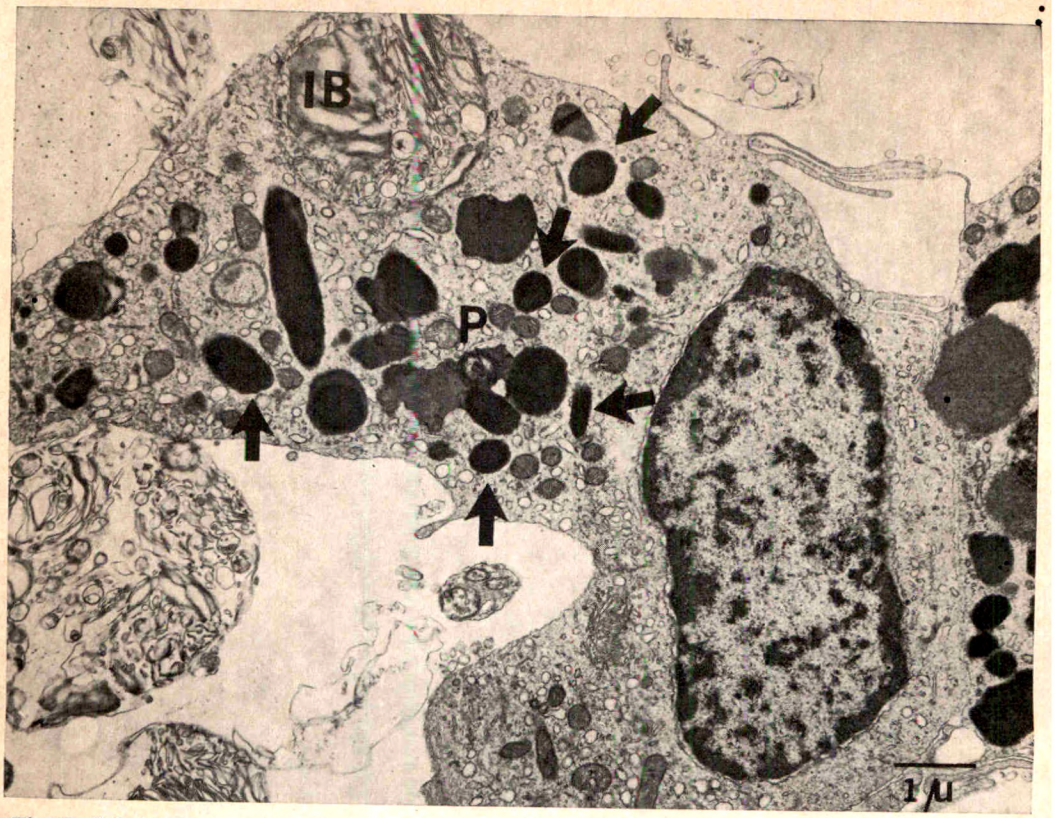


Fig. 2 (Machemer and Laqua). Macrophage in the outer segment layer containing pigment granules lying freely in the cytoplasm (arrows) or in phagosomes (P). A lamellar inclusion body (IB) represents phagocytosed outer segment material. Same specimen as in Figure 1 (×10,850).

cells were settled on the retinal surfaces. However, cell junctions were never seen.

Sometimes the cells appeared in clusters. They were loosely arranged or densely packed with histologically indistinguishable cell boundaries. Typically the clustered cells had variable amounts of pigment granules in their cytoplasm; some were heavily pigmented, others had few or no pigment granules (Fig. 3). Unfortunately, it was not possible to study these cells in cluster formation electron microscopically since the loosely attached clusters were lost during processing of the specimens.

The described single cells could be found as early as one hour after production of retinal detachment directly underlying the retina. Later they became abundant. An initial peak was found between the third and seventh day. All areas of detached retina did not necessarily show the same amount of cells and the number varied in different eyes. The cells appeared intravitreally and preretinally a little later than subretinally. They were mostly found along surfaces such as the retinal surface and along vitreous surfaces. Some were seen in the vitreous cavity itself. The first clusters formed around the seventh day. In any case, these cells were a typical feature of all retinal detachments, including the oldest detachments.

Of great interest was the uptake of radioactive thymidine in these cells. The earliest labeled cells were seen after three days and the label reached a definite peak on the seventh day. In some eyes, thymidine uptake may have been so high that up to 24% of subretinally located cells were labeled (Figs. 3 and 4). In general, the number of labeled cells decreased in older detachments, but variation was considerable.

It is somewhat difficult during experi-

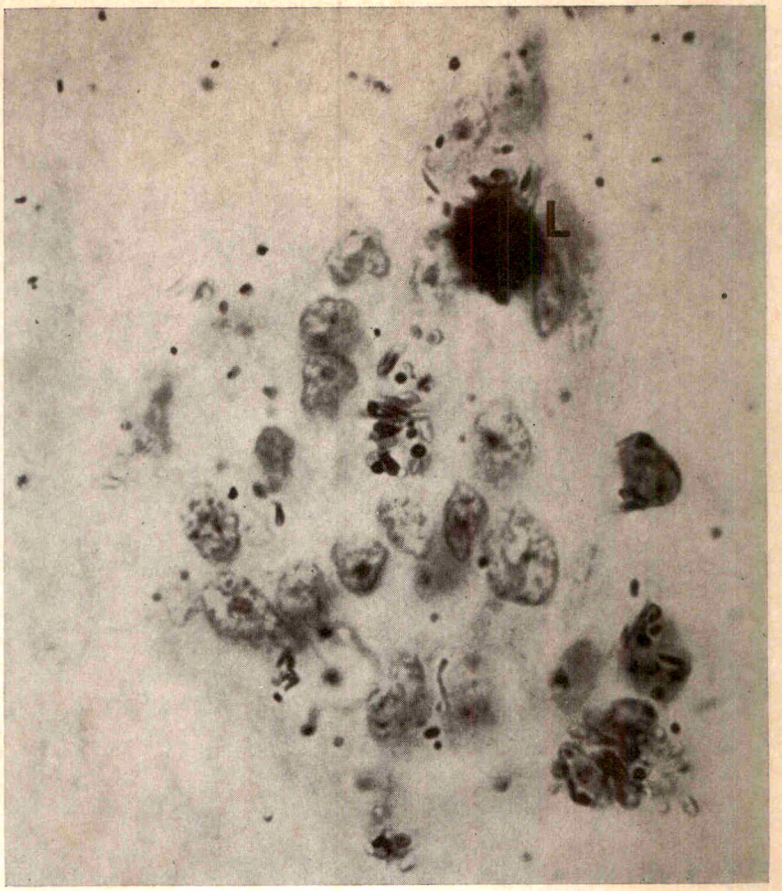


Fig. 3 (Machemer and Laqua). Cluster of subretinal cells with variable pigment content. Labeled cell (L) demonstrates DNA synthesis. (Since the focus is on cells, the overlying silver grains are out of focus). Autoradiograph of paraffin section, 10-week-old detachment.

mental retinal detachment to find the exact time when the above-described cells appear first. Since a retinal wound is purposely created, it is unavoidable that in the early stages of detachments there are blood components around the retinal hole. White blood cells may be mistaken for the above-described cells. However, white blood cells have a smaller and denser nucleus and are not pigmented. Hyalocytes can easily be differentiated from the single pigmented cells. Hyalocytes have an elongated nucleus, are parallel to the retinal surface, and have ill-defined cytoplasm; also, they are rarely labeled. A few eyes (seven) showed a slight inflammatory reaction between 18 hours and three days. The inflammatory cells definitely are different from the round macrophages.

Second cell type: fibrocyte-like cells—Underlying the retina, preretinally, and in the vitreous cavity, cellular membrane formation was observed in retinal detachment. Early stages of this type of proliferation showed loosely arranged clusters of pigmented cells. Between the typical previously described round cells, we found a few spindle-shaped cells with oval nuclei and pigment granules in the cytoplasm. Cells were connected to each other and formed a minute strand (Fig. 5) or a definite membrane. Subretinally, the membrane may be only one or two layers thick, but can be multilayered, consisting of densely packed cells with oval nuclei and with all degrees of pigmentation. Preretinal membranes were localized or covered large areas of the retina (Figs. 6 and 7). Cell shapes varied from spindle-shaped (Fig. 6) to long stretched cells (Fig. 7). The cells lay directly on the retinal surface (Fig. 7) or there was some amorphous or filamentous material between the cells and the retinal surface (Fig. 6). Some cells were densely

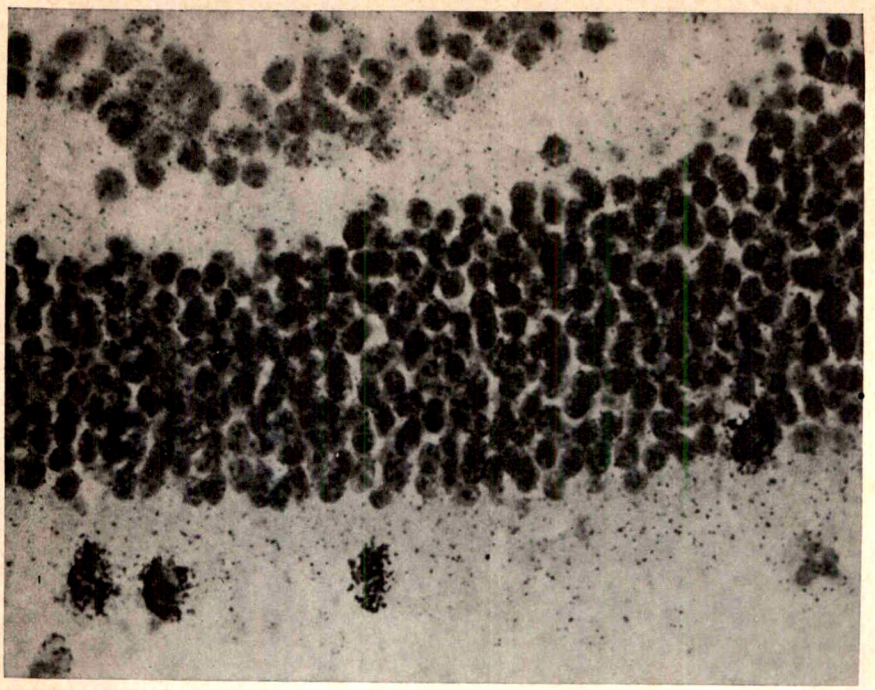


Fig. 4 (Machemer and Laqua). Many macrophages under the retina and in the outer segment layer are labeled as a sign of DNA synthesis. Autoradiograph of paraffin section, 1-week-old retinal detachment.

packed; others had amorphous material between them (Fig. 6). Usually the retina itself was affected by these preretinal membranes with either crinkling of the internal limiting membrane or folding of the whole retina (Figs. 6 and 7).

Intravitreal membranes were found either along the posterior vitreous surface, the posterior lens surface, or around old erythrocyte accumulations.

The electron microscope revealed the epithelial character of these cells: basement membranes and cell junctions (zonula occludens and desmosomes). The cells could be heavily interdigitated by long cytoplasmic processes. The cytoplasm often contained bundles of parallelly arranged filaments and occasional pigment granules. The intercellular space was filled with fibrillae that often showed a periodicity suggestive of collagen (Fig. 8).

First membrane formation was seen around the second week and after four weeks some type of membrane could be found in the majority of eyes with retinal detachment (76.5%, Table 2).

Thymidine labeling demonstrated active proliferation (Fig. 9). A first peak was found four weeks after production of a retinal detachment, but many eyes showed some proliferation even up to 12 weeks. Also, labeling varied considerably in different eyes with similar detachment situations. Radioactive labeling was usually rare in old detachments.

Whenever a retinal detachment extended beyond the ora serrata and detached the

TABLE 2

TIME RELATIONSHIP OF PROLIFERATIONS IN RETINAL DETACHMENT EXCLUDING PROLIFERATIONS OF MACROPHAGES

Duration	No. of Eyes	%
1 hr to 3 days	0/31	0
1 wk to 3 wk	6/17	35
1 mo to 27 mo	65/84	76.5

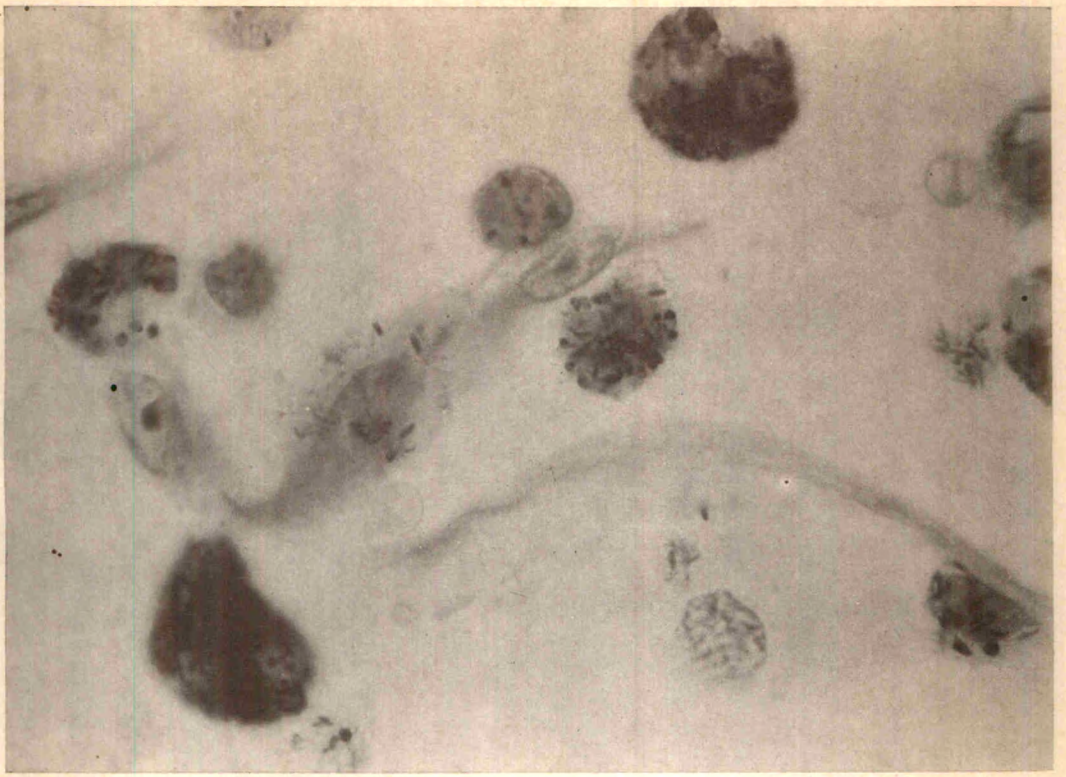


Fig. 5 (Machemer and Laqua). Spindle-shaped cells, often slightly pigmented, appear in a cluster of macrophages and form a minute strand. Paraffin section, intravitreal cell cluster in 4-week-old retinal detachment.

layer of unpigmented epithelium of the pars plana, the underlying monolayer of pigment epithelium reacted by proliferating. There were mounds of these proliferations at the ora serrata which were found as early as seven days after production of a retinal detachment (Fig. 10). Some consisted of a double or triple layer of cells, while others filled the space under the detached pars plana epithelium as if a wedge were driven between pigmented and unpigmented epithelium (Fig. 11). Pigmentation of these cells was usually heavy at the base and light toward the top of the mound. The pigment granules appeared round and were similar in size to those seen in the pigmented cells of the pars plana. Some proliferations continued to extend beyond the pars plana area into the vitreous cavity, forming a membrane that extended toward the inside of the eye along the posterior surface of the vitreous cavity (Fig. 12). These membranes had the same histologic characteristics as vitreous membranes.

Electron microscopy revealed cells with an epithelial character (Fig. 13). They formed basement membranes and were connected to each other by cell junctions, such as desmosomes and zonula occludens. These epithelial cells contained round pigment granules and often bundles of cytoplasmic filaments. In some areas the cells were densely packed; in others, the space between the cells was filled with collagen fibrils.

Cells were radioactively labeled as early as seven days after production of the retinal detachment (Fig. 10), and labeled cells could be seen up to 17 weeks. Proliferation may become stationary at any age of the retinal detachment.

Cells were often either loosely attached to or freely floating over the proliferating pigment epithelium of the pars plana (Fig. 10).

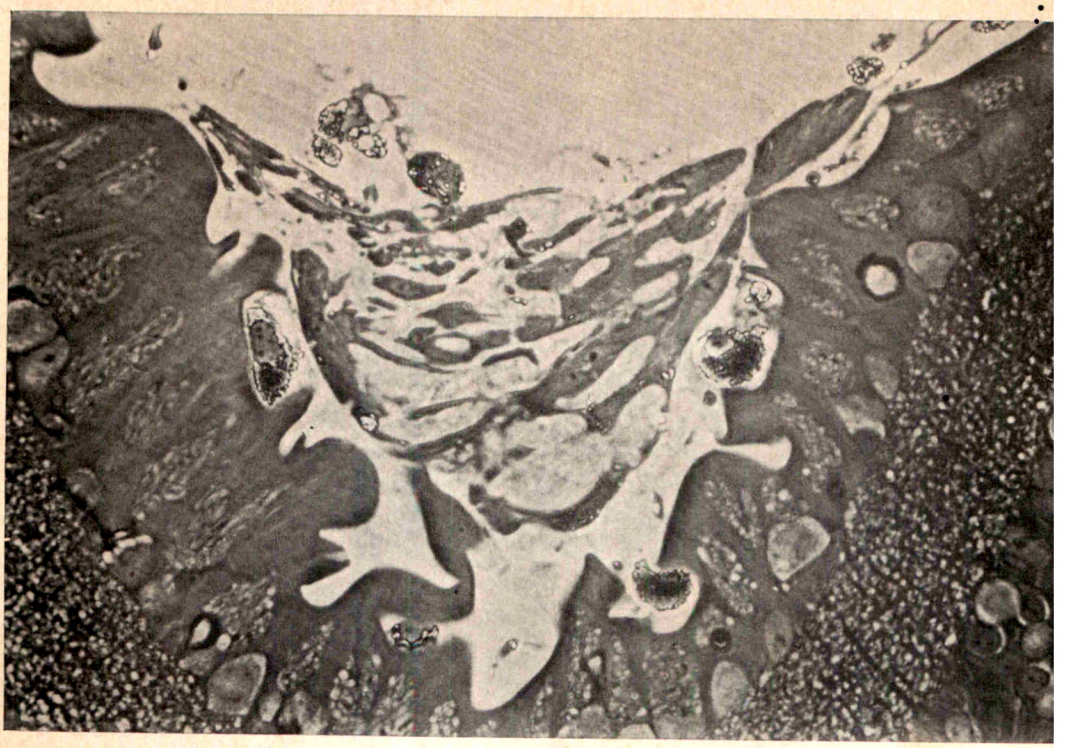


Fig. 6 (Machemer and Laqua). Localized preretinal cell proliferation of mostly spindle-shaped cells with some pigment granules in the cytoplasm. Amorphous or filamentous material lies between cells. Interspersed are round macrophages. Crinkling of the inner retinal layers and folding of the retina is visible; 1-μ section, phase contrast, 9-week-old retinal detachment.

Pigmentation was varied and the pigment granules were similar in size and shape to those found in the underlying cell mound. As early as seven days after production of retinal detachment, the loose cells were found labeled. Unfortunately, it was not possible to examine the loose cells electron microscopically because, in all specimens collected, the cells were washed away during processing.

Another peculiar type of intravitreal membrane was found in some eyes. It appeared as if strand formation consisted of long, multinucleated cells. All these cells seemed to be polarized with a sharply defined border on one side of the cell and veil-like material on the other side, which stained positive for collagen. In old detachments excessive production of this material could be found either as a collagenous veil on one side of the membrane (Fig. 14) or as a finger-like protrusion into the vitreous cavity, where the collagenous center was surrounded by cells. Since these membranes are rare, no electron microscopic examination was possible.

Proliferative activity of these membranes was high, documented by an extremely high labeling index with practically every third or fourth nucleus showing DNA synthesis; many mitoses were seen.

Third cell type: pigment epithelium cells—A third distinct type of cells was found on the inner retinal surface, in the vitreous cavity, and along the posterior surface of the lens. The cells were relatively large with convex, scalloped apices. Their bases were tightly connected to the underlying surface. The apical part of the cell had an ill-defined transparent corona. Pigment granules appeared to cover part of the cells. The granules were often fine and dust-like, but some were larger and were distinctly round and brown. The nuclei of these cells were fairly large,



Fig. 7 (Machemer and Laqua). A monolayer of long, stretched cells covering a large area has heavily folded the internal limiting membrane and created a fixed fold of the retina; 1-μ section, phase contrast, 16-week-old retinal detachment.

round to oval, and not dense. The cytoplasm was clear. As long as these cells were monolayered they did not significantly crinkle the retina (Figs. 15 and 16).

With a slight variation, the same type of cell was found in multilayered preretinal strands, this time with tubule formation. These tubular membranes could fold the whole retina (Figs. 16 and 17).

Electron microscopically these cells were distinctly polarized. At the base of the cell there was a basement membrane with infoldings into which the basement membrane followed. They were intimately connected with the basement membrane of the retina by filamentous material with periodicity suggestive

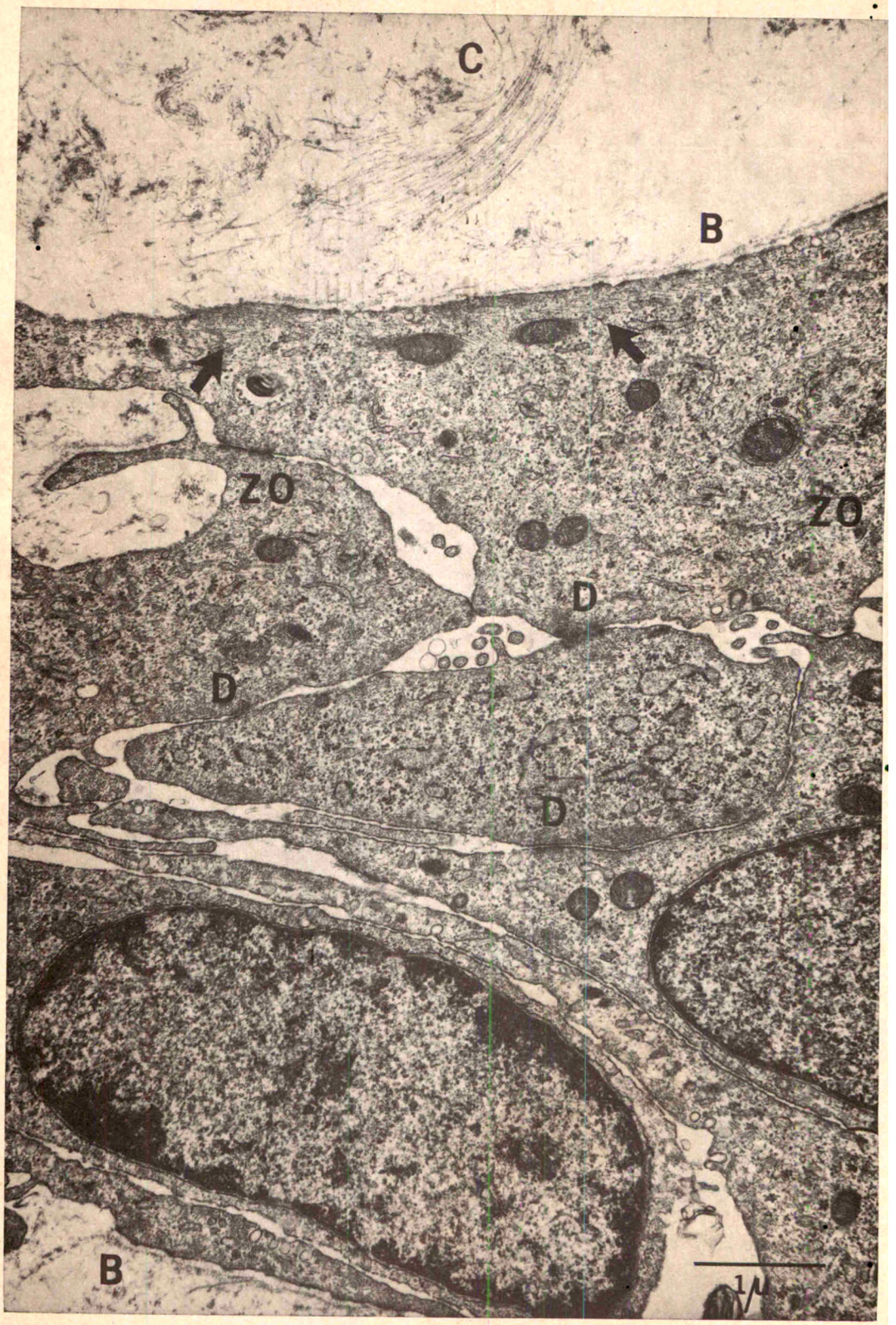

C
B
ZO
ZO
D
D
D
B
1μ

Fig. 8 (Machemer and Laqua). Preretinal membrane. The epithelial character of the cells is demonstrated by basement membranes (B), desmosomes (D), and zonula occludens (ZO). Collagen (C) is deposited between cells. In the cytoplasm are bundles of filaments (arrow). Same specimen as Figure 6 (×21,250).

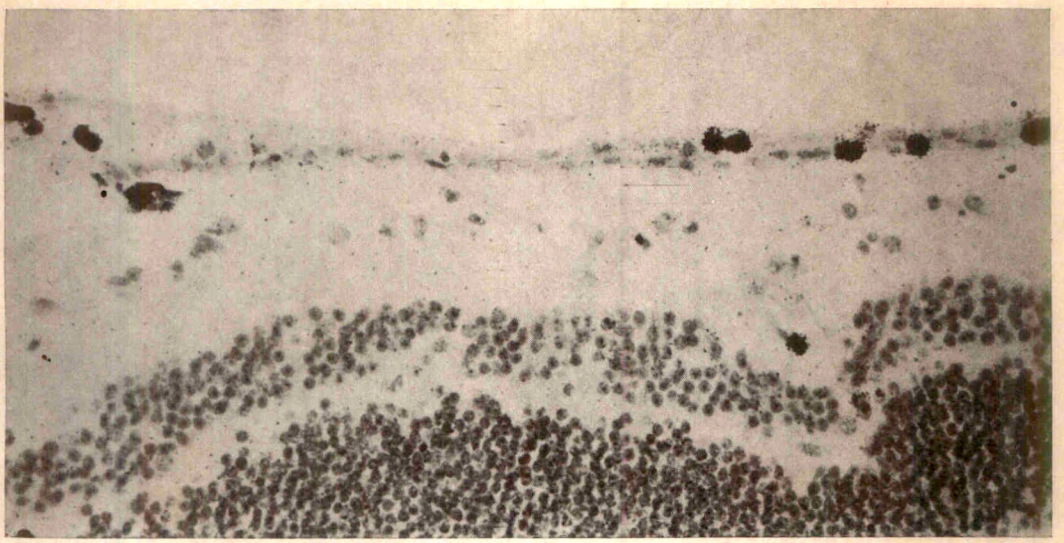


Fig. 9 (Machemer and Laqua). Heavy label of preretinal membranes demonstrates active proliferation. Autoradiograph of paraffin section, 5-week-old retinal detachment.

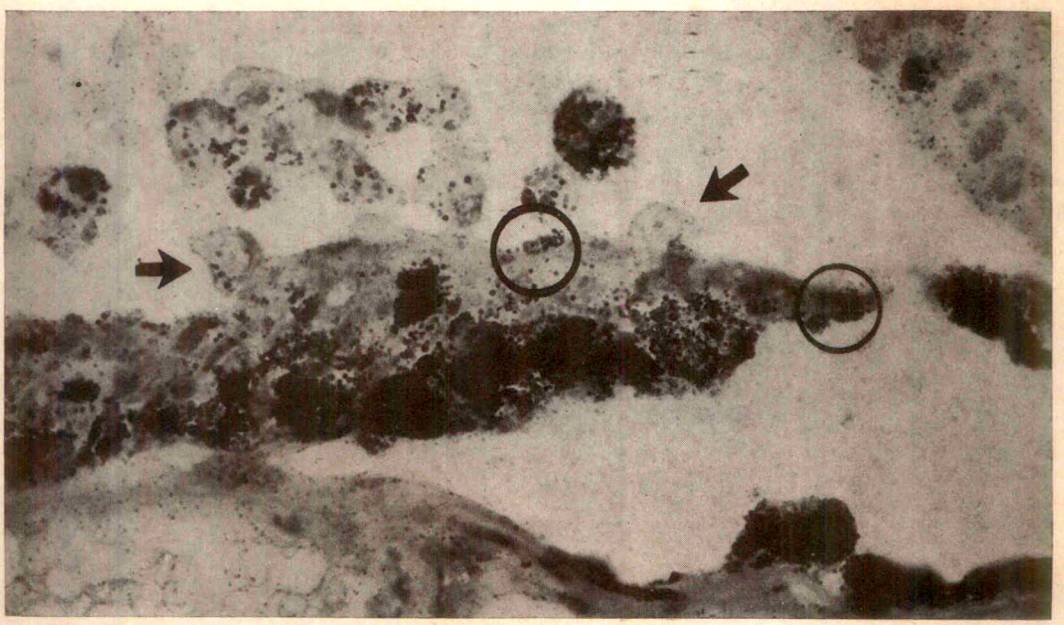


Fig. 10 (Machemer and Laqua). Flat mound of proliferated cells at ora serrata. Two (circled) cells are labeled. (The label is difficult to see because of heavy pigmentation of cells.) Several cells seem to migrate out of the mound (arrows). Round, pigmented cells are floating freely over the mound. Autoradiograph of paraffin section, 2-week-old retinal detachment.



Fig. 11 (Machemer and Laqua). Proliferated pigment epithelial cells under detached pars plana epithelium at ora serrata. Gradual loss of pigmentation is obvious; 1-μ section, 9-week-old retinal detachment.

of collagen. The cells were connected to each other by junctional complexes. The apical parts of the cells consisted of a multitude of fine microvilli. Pigment granules were not found in these processes but appeared only in the upper parts of the cell. Many mitochondria were seen but no inclusion bodies were found (Fig. 18). These cells resembled in all aspects normal retinal pigment epithelium. When they were arranged in a tubular fashion the microvilli are oriented toward the lumen (Fig. 17).

They were found not earlier than four weeks after retinal detachment and were usually detected in long-standing detachments. They were not common and radioactive labeling with thymidine was not found.

Transitions were found between the two types of epithelial membrane-forming preretinal cells. An example is given in Figure 16, which shows a 17-week-old detachment: tubular arrangement of pigment epithelial cells, a monolayer of pigment epithelium cells, and immediately adjacent multilayered, loosely arranged fibrocyte-like cells are all found together in a small area of detached retina.

Observations at pigment epithelium layer—Following a retinal detachment the cells of the pigment epithelium showed typical changes: the basic cuboidal pattern was retained but the apical part became scalloped. The pigment-free corona, representing microvilli originally interdigitating with the outer segments of the retinal photoreceptors, became visible. The nucleus remained in the base part of the cell[5,6] (Fig. 19). Whereas in normal pigment epithelium, proliferative activity is extremely rare (R.M., unpublished data), in retinal detachment the pigment epithelial cells can often be radioactively labeled. This was most prominent between seven days and eight weeks (Fig. 19).

In some areas changes suggested that the pigment epithelium may have migrated toward the subretinal space (Fig. 19): a

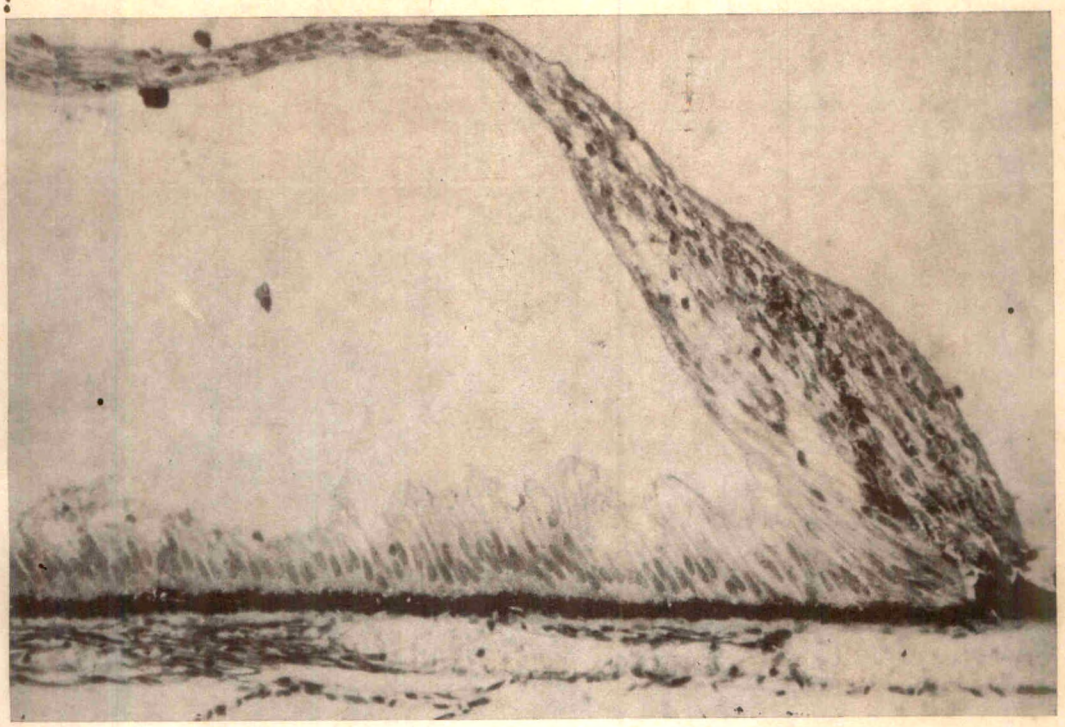


Fig. 12 (Machemer and Laqua). Proliferated pars plana pigment epithelium with extension into the vitreous cavity. The membrane follows the posterior vitreous surface. Paraffin section, 8-week-old retinal detachment.

mushroom-like pigment epithelial cell protruded beyond the normal height of the pigment epithelial cell layer. The nucleus was no longer in the base; instead, it was found in the top of the mushroom. There seemed to be no attachment of this cell to Bruch's membrane since the nuclei of neighboring cells were close to each other. This phenomenon was seen as early as one hour after production of a retinal detachment and as late as ten weeks. Also, the pigment content of some cells appeared to be decreased (Fig. 19). Although carefully looked for, no cell was ever found to migrate through Bruch's membrane into the pigment epithelial layer and from there into the subretinal space.

Often, round cells, singly or in clusters, were found immediately overlying the pigment epithelium as early as 12 hours after retinal detachment. These cells looked similar to cells seen in the subretinal, preretinal, and intravitreal space. These cells showed radioactive labeling beginning as early as seven days after production of retinal detachment, and even in late detachments proliferative activity was evidenced by radioactive labeling, thus explaining why these clusters could reach considerable size.

When retinal detachments were experimentally created, a small area of the pigment epithelium was denuded.[1,5] Three days later this area was covered by cells. There may be just a monolayer or the cells may be lying loosely on top of each other. Almost all cells contained wedge-shaped pigment granules. Some pigmented cells seemed to float freely in the subretinal fluid over the pigment epithelial wound. Intense labeling (Fig. 20) and mitoses demonstrated the heavy ongoing proliferative activity resulting in mounds and tongue-like protrusions of considerable size as early as two weeks after production of retinal detachment.[5]

Normal-appearing pigment epithelium may have been covered by a sheet of several layers of long, stretched, pigmented cells containing



Fig. 13 (Machemer and Laqua). Proliferation at ora serrata. Note the epithelial characteristics of cells with basement membranes (B), desmosomes (D), and zonula occludens (ZO). Free pigment granules in cytoplasm (P), cytoplasmic filaments (inset). Same specimen as in Figure 11 (×20,200; inset, ×48,000).

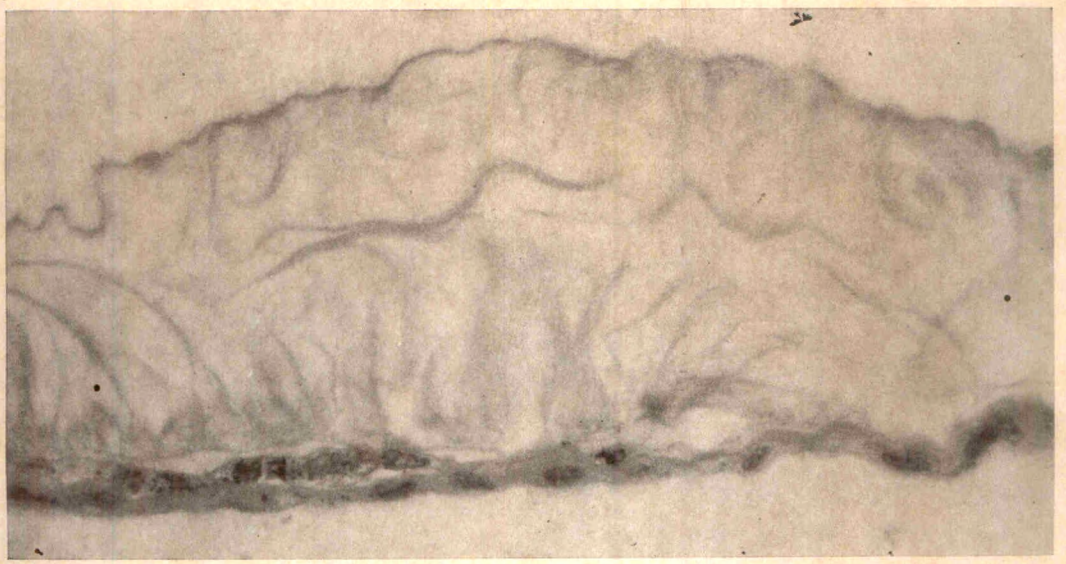


Fig. 14 (Machemer and Laqua). Intravitreal strand of cells producing large amounts of collagen. Paraffin section, Mallory stain, 17-week-old retinal detachment.

flat nuclei. This tissue stained positive for collagen (Fig. 21). In other eyes a mound of cells was found that was heavily pigmented at the base and less pigmented at the top. The mound was covered by a monolayer of pigmented cells that had the exact appearance of retinal pigment epithelium when the retina was detached (Fig. 22). All these formations resembled those found elsewhere in the eye during retinal detachment.

Discussion

The described experiments demonstrate that in almost all eyes with experimental retinal detachment new cells appear and proliferate under and on the retina, in the vitreous

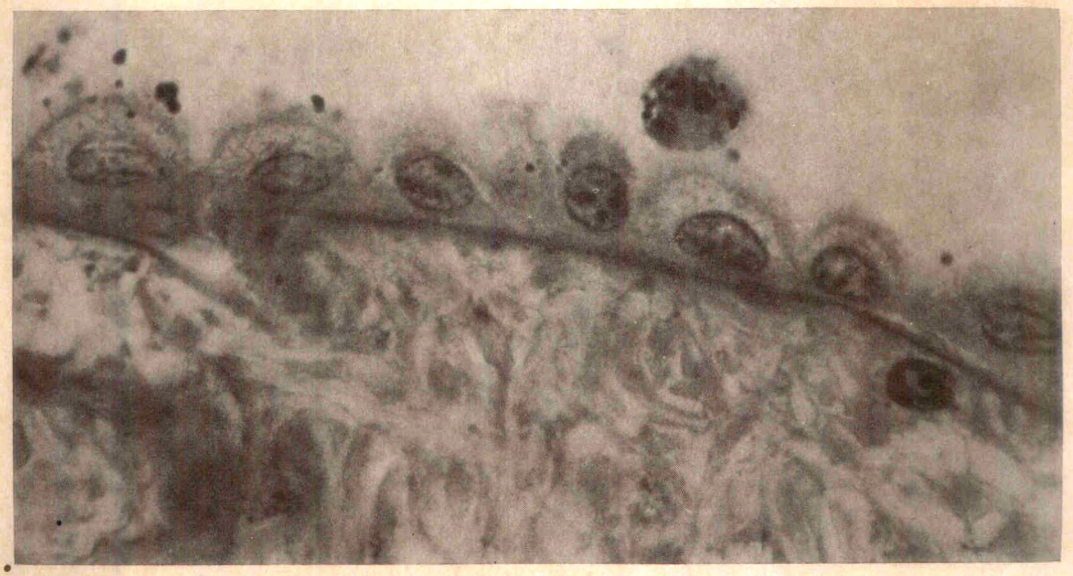


Fig. 15 (Machemer and Laqua). Preretinal monolayer of cells similar to pigment epithelium in retinal detachment. Compare with Figure 19. Paraffin section, 4-week-old retinal detachment.

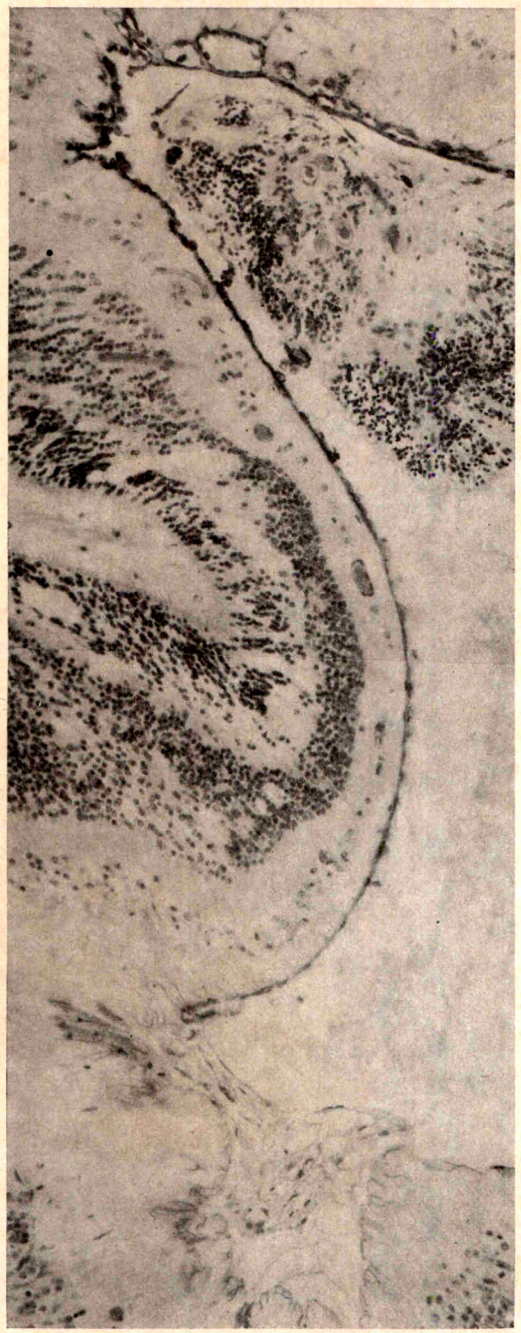


Fig. 16 (Machemer and Laqua). Variety of preretinal proliferations: top, tubular arrangement of pigment epithelial cells; middle, monolayer of pigment epithelial cells; bottom, fibrocyte-like cells. Paraffin section, 17-week-old retinal detachment.

cavity, at the ora serrata, and at the level of the pigment epithelium. These cells have typical characteristics.

The first cell type is a rather large, often pigmented cell which is usually found singly but sometimes accumulates in clusters. These cells act as macrophages. The second and third cell types form membranes. Both have epithelial cell characteristics with formation of basement membranes and cell junctions. The second bears some similarity to fibrous tissue; the third appears to be identical to retinal pigment epithelium.

The question now arises, from where do these cells derive? We believe the pigmented single or clustered cells that act as macrophages derive from the retinal pigment epithelium. The following data support this conclusion.

Two experiments were designed to solve the question of the inherent capabilities of proliferating pigment epithelium. Pigment epithelial cells from one eye were injected into the vitreous cavity of the other eye,[2] or brought into cell-tight diffusion chambers and were then transplanted into the vitreous cavity of the other eye.[3] Both experiments demonstrated the appearance of pigmented macrophages with electron microscopic features identical to those found in experimental detachment. The development of this cell type in a cell-tight diffusion chamber excludes any other origin except the pigment epithelial cell itself.

The following arguments further support pigment epithelial origin:

1. Cells were observed that left the layer of the pigment epithelium or separated from the proliferating mound at the ora serrata to migrate into the subretinal space (Figs. 10 and 19).

2. The loss of cells in the pigment epithelial layer due to migration is obviously compensated for by increased multiplication (Fig. 19).

3. The wedge-shaped pigment granules in the phages are identical to those seen in pigment epithelium. Round pigment granules in

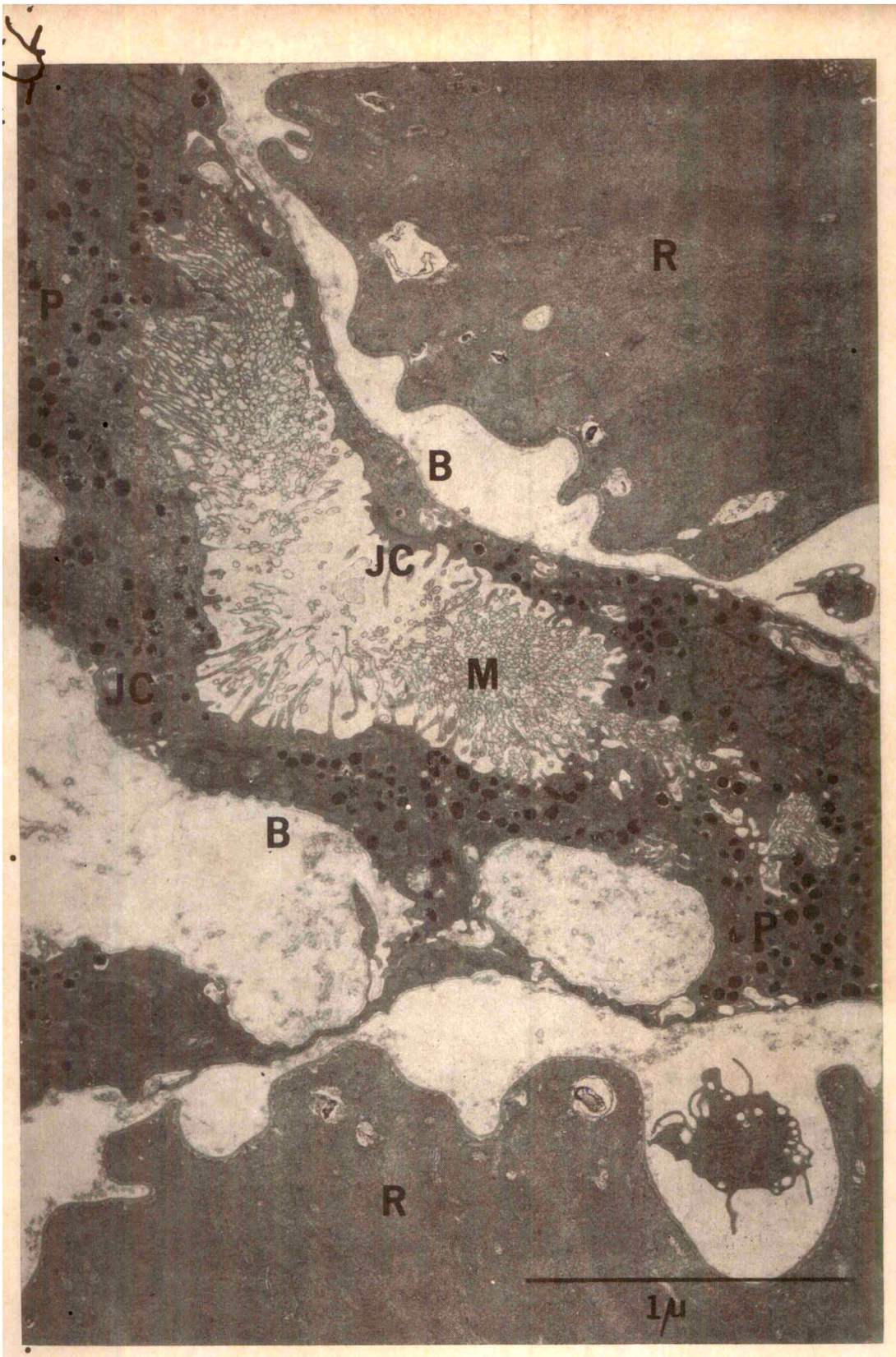


Fig. 17 (Machemer and Laqua). Tabular arrangement of preretinal polarized cells folding the retinal surface. B indicates polarized cell with basement membrane and basal infoldings; JC, junctional complexes; M, microvilli; P, free pigment granules; R, edematous detached retina. 9-week-old retinal detachment (×10,000).

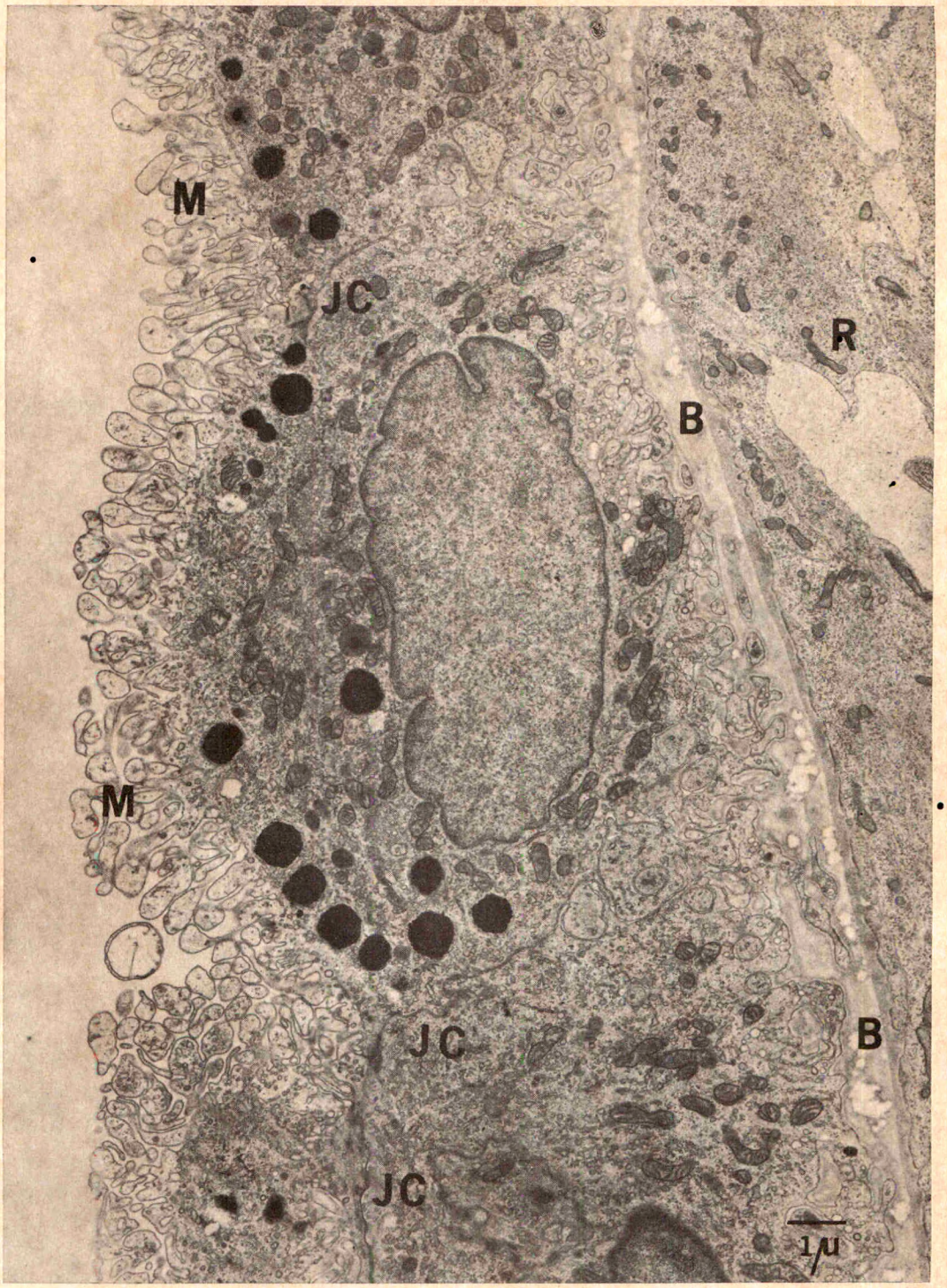


Fig. 18 (Machemer and Laqua). Preretinal pigment epithelium cells. Polarized cell with basement membrane and basal infoldings (B), junctional complexes (JC), microvilli (M), and edematous detached retina (R); 8-month-old retinal detachment (×7,150).

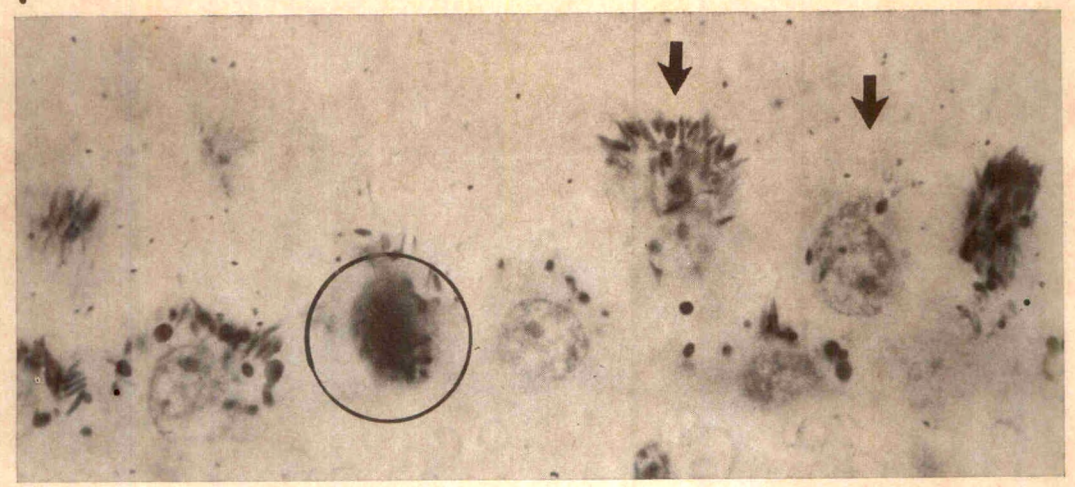


Fig. 19 (Machemer and Laqua). Pigment epithelium under detached retina. Note the scalloped appearance of the cells. Label (circle) indicates DNA synthesis (since the focus is on the cells the overlying silver grains are out of focus). Sparcity of pigment granules in some cells is probably a sequela of cell division. Some cells (arrows) seem to leave the pigment epithelial layer. Autoradiograph of paraffin section, 4-week-old retinal detachment.

macrophages probably derive from cells that liberated themselves from the ora serrata. Only some of the pigment granules in the macrophages are found to be contained in phagosomes, often together with other phagocytosed material. Most pigment granules lie freely in the cytoplasm or are surrounded by a tightly fitting envelope (Fig. 2).

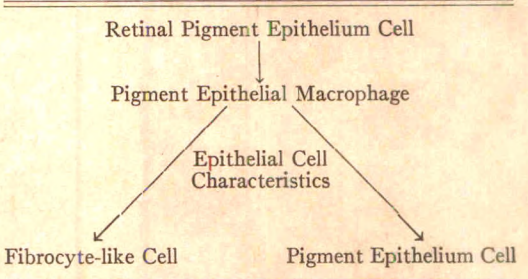
4. The phagocytotic activity normally performed by pigment epithelium is continued by the macrophages. Cells that derive from the pigment epithelium are first found under the retina phagocytosing outer segment material,[6] just as they have done while in contact with the retina during retinal attachment[7] (Fig. 2). Cells that are not lying under the retina and are unable to phagocytose outer segment material either have few phagosomes or contain in their phagosomes other cell debris, such as erythrocytes.

It appears, therefore, that the highly specialized epithelial cells of normal pigment epithelium have a peculiar pathway (Table 3) the first step of which is a de-differentiation into a macrophage. To avoid confusion with macrophages of different origin but to point out the similarities, we wish to call this cell "pigment epithelial macrophage," as proposed by Gloor.[8]

These cells are a typical feature of retinal detachment. Since they appear so early in retinal detachment and multiply greatly by the third day, there must be a strong stimulus for their production (Fig. 4). This unknown factor may be the aged outer segment material itself, together with other cell debris such as old erythrocytes. Obviously, some of the macrophages finally settle down singly or in clusters, possibly without further phagocytosis.

TABLE 3

POSSIBLE PATHWAY OF DEVELOPMENT OF RETINAL PIGMENT EPITHELIAL CELL IN RETINAL DETACHMENT



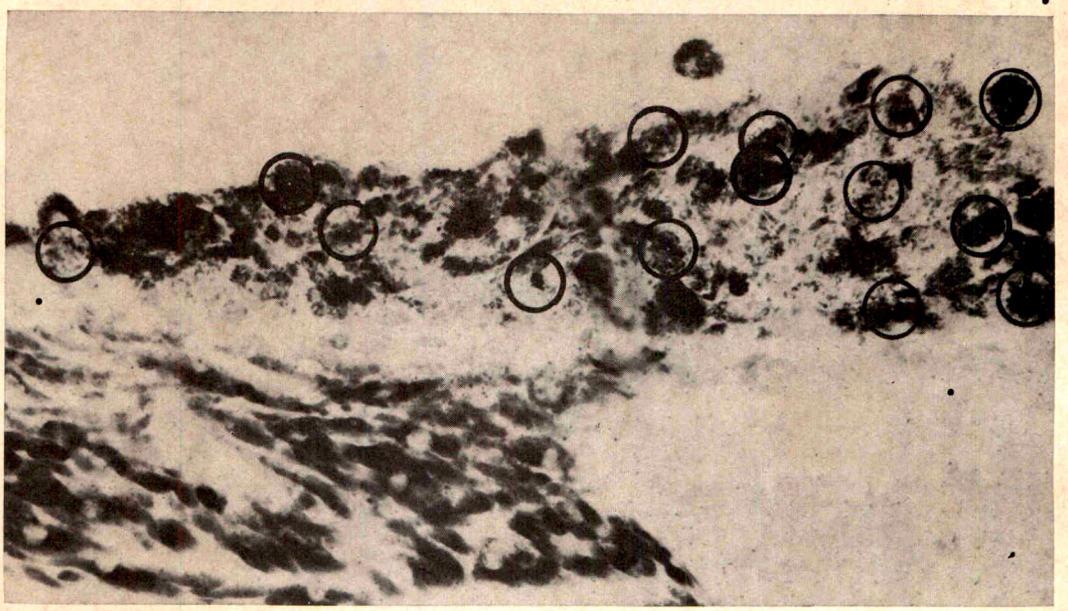


Fig. 20 (Machemer and Laqua). Heavy proliferation at pigment epithelium level under detached retina at experimentally created pigment epithelium defect. Note the many labeled cells (circles). The label is difficult to see because of heavy pigmentation of many cells. Autoradiograph of paraffin section, 1-week-old retinal detachment.

That pigmented macrophages derive from pigment epithelium was studied specifically in Coats' disease.[9-11]

The next two cell types found in experimental retinal detachment show so definite epithelial cell characteristics that this excludes their origin from histiocytes, fibroblasts, or blood cells which are all of mesodermal origin and usually do not form cell junctions and basement membranes. Instead, there is experimental evidence that cells deriving from the pigment epithelium, an ecto-

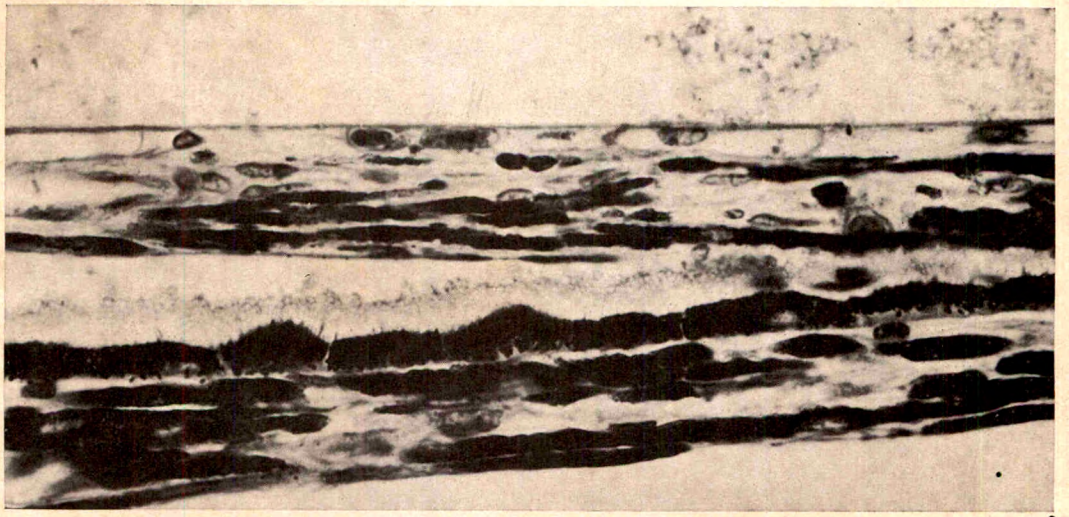


Fig. 21 (Machemer and Laqua). Collagenous tissue with partly pigmented cells overlying pigment epithelium near previous pigment epithelium defect. Paraffin section, 14-week-old retinal detachment.



Fig. 22 (Machemer and Laqua). Mound of proliferated pigment epithelial cells covered by scalloped cells at site of previous pigment epithelial defect. Note similarity to Figures 15 and 19. Paraffin section, 27-month-old retinal detachment.

dermal structure, can produce cells identical to those found in retinal detachment. The previously mentioned experiments[2,3] with autotransplantation of pigment epithelial cells into the vitreous cavity showed this clearly.

The following arguments further support the pigment epithelial origin of the two types of epithelial cells:

1. Cell characteristics found in preretinal and intravitreal proliferation are identical to those found at the ora serrata (Figs. 8 and 13). This is of special importance since cells known to be in direct contact with the pigment epithelium show no difference from the cells proliferating without contact with the pigment epithelium.

2. There is a striking histologic and electron microscopic similarity between highly differentiated pigment epithelium cells growing on the retinal surface, in the vitreous cavity, or behind the lens, and the cells found in the layer of the pigment epithelium itself (Figs. 15, 18, and 19).

3. There is a striking morphologic similarity between intraocular proliferations and reactive proliferations at the pigment epithelial layer (Figs. 3, 7, 15, 20, 21, and 22).

4. Many of the proliferated cells contain free pigment. The pigment content may be low, until finally no pigment is found. Due to continuous multiplication, daughter cells lose more and more of their pigment content until they are finally pigment-free (Figs. 2 and 3).

From these observations we must conclude that the next step in the metaplasia of the pigment epithelial cell consists of a re-differentiation of the pigment epithelium macrophage into a cell that bears histologically great similarity to a fibrocyte (Table 3). Yet, electron microscopy demonstrated definitely that this cell is not a fibrocyte but a cell with epithelial characteristics (Figs. 5, 6, and 8). To point out the similarities with fibrocytes but to avoid the implication that these cells are of mesodermal origin, we call these cells "fibrocyte-like cells." This "fibrous metaplasia" of pigment epithelium has been suspected by many investigators.[8,9,11-15] Preretinal and retroretinal membrane formation presumably deriving from pigment epithelium was discussed by others as well.[16,17]

The fibrocyte-like cells show multiplication later than the macrophages and there is a great variety in the amount of proliferation in different eyes. Yet the fact that most eyes show some signs of proliferation (Table 2) is a strong indicator for a stimulating factor that exists in practically all eyes. It is not known what stimulates the fibrocyte-like

cells. It is also unknown why some eyes have excessive proliferation with formation of stiff retinal folds and visible vitreous membranes and others have so little.

A specific stimulation seems to exist at the ora serrata; probably it is the detachment of the unpigmented epithelium of the pars plana itself because proliferation is limited to the area underlying the unpigmented epithelium and is found only when the pars plana epithelium is detached (Fig. 10). This area is known to react heavily with proliferation. For example, the Ringschwiele, described by the pathologist in long-standing retinal detachments,[16,18] is only the excess of what is found in any retinal detachment where the detachment has extended anterior to the ora serrata.

Another developmental direction a pigment epithelial macrophage can take appears to be a full, re-differentiation to an epithelial cell with all the features of pigment epithelium (Table 3). We propose to call this cell type "pigment epithelium cell" (Figs. 15, 17, and 18). Intact pigment epithelial cells seem to be washed off the pigment epithelial wound at the time of production of the retinal detachment and, after passing through the retinal hole, settle unchanged on the retinal surface. However, pigment epithelium cells appear only late in retinal detachment (about the fourth week) and often in large amounts (Fig. 16), refuting this statement. Since proliferation of the pigment epithelium is stimulated as early as seven days, one wonders why pigment epithelium cells are found so late if they are actually derived directly from displaced pigment epithelium cells. Tubular arrangement of growing pigment epithelium cells is not unknown and has been observed in tissue cultures,[19] and neoplastic pigment epithelial lesions.[20]

Finally, the question arises of where membrane formation will occur in the posterior eye. It is known from tissue cultures, and one can consider the eye in retinal detachment an in vivo tissue culture, that cells settle on and proliferate along available surfaces. Therefore, in the case of retinal detachments, membrane formation can be expected along the inner and outer surface of the retina, any vitreous surface, and the posterior lens surface. Single macrophages are capable of actively migrating between the inner and outer segments of detached retina or into the formed vitreous cavity, as evidenced by the clinically visible "tobacco dust."[21]

The factors that lead to contraction of these membranes and the importance of collagen deposition will be subsequently discussed.

The study of experimental retinal detachment leads us to believe that intraocular proliferation of cells results in massive formation of single or clustered macrophages (found in all retinal detachments) and membrane formations by fibrocyte-like cells and pigment epithelium cells (found in 76.5% of all detachment eyes four weeks or older). This membrane formation takes place on all available surfaces such as the upper and under surface of the retina, vitreous surfaces, or the posterior lens surface, and at the ora serrata. As could be demonstrated, many of the proliferations originate from pigment epithelial cells. It should be emphasized that glial proliferation participates in this process.[4] It is these membranes that cause wrinkling of the retinal surface, folding of the whole retina, or membrane formation in the vitreous cavity. We propose to call this entity "massive periretinal proliferation (MPP)."

Summary

Cell proliferation and membrane formation found in the posterior parts of the eye after production of retinal detachment in owl monkey eyes had either the characteristics of macrophages or of membrane-forming epithelial cells. The proliferating cells originated from pigment epithelium. These membranes caused folding of the retina and strand formation in the vitreous cavity. Since cell proliferation was present on all available

surfaces, such as the upper and under surface of the retina, and along vitreous surfaces, we propose to call this entity "massive periretinal proliferation" (MPP).

ACKNOWLEDGMENTS

We thank Mrs. Marcilia Halley, Mr. Ernest Reeves, and Mr. Wayne Hinecker for their help in the animal evperiments; Mrs. Marcilia Halley for histologic and electron microscopic work; Ms. Barbara French for photographic assistance; Ms. Reva Hurtes and Dwain Fuller, M.D., for editorial assistance; and Mrs. Charlaine Rowlette for secretarial assistance.

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RESULTS AND COMPLICATIONS OF 100 CONSECUTIVE CASES OF PARS PLANA VITRECTOMY

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Vitreous surgery using a pars plana approach is rapidly becoming a widely practiced procedure. Recently, several vitrectomy instruments were developed[1-8] and the surgical technique was described.[9-11] The pars plana vitrectomy technique provides a method of surgical therapy for certain otherwise inoperable ocular disease states and offers an alternative approach to other conditions. Several indications have evolved for this procedure (Table 1).[11-15]

The recent growth of elective, direct surgery on the vitreous body represents a significant departure from conventional ophthalmic surgical principles. Because of the nature of the procedure, a significant risk of complications is involved. Therefore, the results and complications of this procedure must be critically analyzed to determine its efficacy and risk in certain clinical situations. We report the indications, short-term results, and complications of 100 consecutive cases of pars plana vitrectomy.

PATIENTS AND METHODS

We performed 145 of the 150 pars plana vitreous surgical procedures done at the Wilmer Eye Institute between March 2, 1973, and Nov. 1, 1974. The initial results were somewhat disappointing; we modified our instrumentation and refined the surgical technique since the first operations. Therefore, we arbitrarily chose to report our most recent 100 consecutive cases with adequate follow-up data.

The 97 patients (100 eyes), ranging in age from 1 to 78 years, consisted of 52 males and 45 females. Three patients had both eyes operated on at different times. The median age was 56 years. Follow-up intervals ranged from two months (seven patients) to 13 months, with a mean and median follow-up interval of seven months.

Each patient underwent a complete preoperative ocular evaluation including a detailed history and examination. Ocular examination included best corrected visual acuity, external and slit-lamp examination, applanation tonometry, slit-lamp evaluation of the

TABLE 1

INDICATIONS FOR PARS PLANA VITREOUS SURGERY

Blindness due to nonresolving vitreous opacities
Certain types of retinal detachment
Recent traction detachment involving the macula
Certain giant tears
Severe vitreous traction preventing successful conventional retinal surgery
Trauma
Certain penetrating injuries
Nonmagnetic intraocular foreign bodies
Vitreous biopsy
Anterior-segment reconstruction
Membranous cataract
Pupillary membrane
Persistent hyperplastic primary vitreous (PHPV)
Other
Vitreous incarceration with persistent Irvine-Gass syndrome
Aphakic vitreous touch with corneal edema
Aphakic pupillary-block glaucoma
Glaucoma, other
Hemolytic
Phakolytic, due to retained lens material
Endophthalmitis

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vitreous body, and examination of the retina with direct and indirect ophthalmoscopy and three-mirror contact lens biomicroscopy where possible. Special sensory testing in low-vision eyes included confrontation perimetry studies, light projection, color (red and green) perception, and testing for the presence of entoptic imagery. Bright-flash electroretinography (ERG) and combined A- and B-scan ultrasonography were done in selected cases. (Bright-flash ERG employs a light flash approximately 100× brighter than the conventional ERG light flash.) Detailed vitreoretinal fundus drawings were made when appropriate, and we obtained fundus photographs when possible.

All operative procedures employed the Machemer[9-11] pars plana vitrectomy technique. We used either the Machemer vitreous-infusion-suction-cutter (VISC) or Douvas Roto-extractor. Retinal cryopexy and intraocular sulfur hexafluoride gas (SF_6) injection, with or without scleral buckling, were used to treat retinal breaks. Separate subconjunctival injections of gentamycin hydrochloride (20 mg) and dexamethasone (2 mg) were given at the end of each operation unless there was a specific history of allergy to the medication.

Patients were usually hospitalized three to five days after surgery and were followed at weekly intervals until the eye was stable. After surgery the eyes were treated with corticosteroids and cycloplegic drops until any intraocular inflammation cleared. We attempted to recall all patients for a follow-up evaluation prior to this report. When patients could not appear we contacted the referring physician for current follow-up data.

Between Nov. 5, 1973, and Oct. 11, 1974, 104 operations were performed but four eyes were excluded from this series because there were inadequate follow-up data. We chose a minimal follow-up interval of two months, but a longer interval was used if the eye had not achieved a stable state, and we could not determine the immediate success or failure of the procedure. The sole criterion of success was visual improvement of at least two lines on the Snellen chart or improvement to a measurable acuity of at least 3/200. However, in selected cases, we performed the operation for indications that did not include possible improvement in vision. In these cases, there was a technical success if the mechanical objectives of the procedure were achieved without complication.

TABLE 2

INDICATIONS FOR VITREOUS SURGERY IN 100 CONSECUTIVE CASES

Complications of diabetes	51
Vitreous opacities (nondiabetic)	10
Trauma	
Penetrating	8
Intraocular foreign body	5
Anterior-segment reconstruction	8
Endophthalmitis	4
Retinal detachment	4
Persistent Irvine-Gass syndrome	3
Vitreous biopsy	2
Aphakic pupillary-block glaucoma	2
Other	3
	100 eyes

RESULTS

Indications for surgery are shown in Table 2. Of the 51 eyes with complications of diabetic retinopathy, 24 had preexisting vitreous hemorrhage without detachment of the posterior retina, six had traction retinal detachment without significant vitreous hemorrhage, and 21 eyes showed both dense vitreous hemorrhage and posterior traction detachment. Of the eight eyes undergoing anterior segment reconstruction, five had membranous cataract, two eyes had persistent hyperplastic primary vitreous humor, and one had a postinflammatory pupillary membrane. The four eyes with retinal detachment included three with massive vitreous retraction (MVR) and one with a giant retinal tear. Seven types of operative procedures were employed (Table 3).

Visual acuity results after surgery are shown in Tables 4 and 5. Table 6 further divides the visual results according to specific

TABLE 3

OPERATIVE PROCEDURE FOR 100 EYES WITH VITREOUS SURGERY

Lensectomy	5
Pars plana vitrectomy	18
Lensectomy and vitrectomy	19
Vitrectomy, cryotherapy, and gas	6
Lensectomy, vitrectomy, cryotherapy, and gas	37
Lensectomy, vitrectomy, scleral buckle, cryotherapy, and gas	13
Vitrectomy and membrane stripping	2
	100 eyes

complications of proliferative diabetic retinopathy. Operations on another four eyes in this series of 100 were technically successful in which the mechanical objectives of the procedure were accomplished without complications. In these eyes, possible visual acuity improvement was not an indication for surgery and acuity did not improve after surgery.

Intraoperative complications are shown in Table 7. The most common location for retinal tears was anterior, near the meridian of the sclerotomy site (19 eyes). Other common locations were sites of firm vitreoretinal adhesion (16 eyes) or dialyses in other quadrants (three eyes). Two eyes developed giant tears. In four eyes the retinal tears resulted in retinal detachment that could not be successfully treated.

Postoperative complications (Table 8) included 21 eyes lost due to rubeosis iridis, phthisis, massive intraocular hemorrhage (during or after surgery), and endophthalmitis. Of these 21 eyes, three had preexisting retinal detachment with MVR and three others were considered prephthisical (after trauma) before the operation. Five other eyes demonstrated rapidly progressive proliferative diabetic retinopathy with extensive neovascularization and progressive traction detachments before surgery.

DISCUSSION

Development of the pars plana vitrectomy technique has added another dimension to ophthalmic surgery. It provides a new capability for dealing with certain disease states and is applicable to many conditions other than blindness due to vitreous hemorrhage. The results in this series illustrate both the usefulness of this procedure and the significant risks and limitations involved.

Appropriate case selection is of major importance and profoundly influences the results of surgery. Visual acuity improvement is dependent on both a technically successful operation and the functional capability of the retina. When the retina is normal in other respects, good visual acuity can be achieved by removing vitreous opacities or opaque material from the pupillary space. However, in most of our cases, preexisting retinal involvement limited final visual acuity. This was uniformly true in diabetic patients although, for some of these patients, a modest improvement in vision was a major contribution to their way of life.

Unfortunately, we have no entirely reliable way to predict the functional capability of the retina in the presence of dense opacities. Generally, the better the response to subjective testing (for example, light projection), the better the prognosis for visual acuity improvement after surgery (although macular scarring may limit central acuity).

TABLE 4

CHANGE IN VISUAL ACUITY AFTER VITREOUS SURGERY IN 100 EYES

	Improved	Same or Decreased
Complications of diabetes	31	20
Vitreous opacities (nondiabetic)	8	2
Trauma		
Penetrating	5	3
Intraocular foreign body	2	3
Anterior-segment reconstruction	8	0
Endophthalmitis	3	1
Retinal detachment	0	4
Persistent Irvine-Gass syndrome	2	1
Vitreous biopsy	2	0
Aphakic pupillary-block glaucoma	1	1
Other	2	1
	64	36

TABLE 5

VISUAL ACUITY AFTER VITREOUS SURGERY IN 64 EYES SHOWING IMPROVED VISUAL ACUITY

	20/20–20/50	20/60–20/200	20/300–3/200
Complications of diabetes	5	10	16
Vitreous opacities (nondiabetic)	—	6	2
Trauma			
Penetrating	1	2	2
Intraocular foreign body	2	—	—
Anterior-segment reconstruction*	4	2	—
Endophthalmitis	2	1	—
Persistent Irvine-Gass syndrome	1	1	—
Vitreous biopsy	1	1	—
Aphakic pupillary-block glaucoma	—	1	—
Other	2	—	—

* Patient with bilateral persistent hyperplasic primary vitreous is too young to measure acuity.

Bright-flash ERG was the most useful special test preoperatively. The bright flash allows the light stimulus to reach the retina through opaque media. No ERG response can be recorded if total retinal detachment is present. A very low response in eyes with attached retina seems to indicate severe intraretinal disease and a poor prognosis for visual improvement. However, in eyes with opaque media, the decision to recommend surgery is based largely on clinical grounds, including the ocular examination, visual needs of the patient, and an estimate of the risks involved.

Eyes with relatively clear media permit a realistic estimate of what can be achieved by surgery. When preexisting retinal detachment was not present, we were successful in biopsies of vitreous infiltrates, excising vitreous from cataract wounds, removing retained lens material, relieving aphakic pupillary-block glaucoma, and removing vitreous abscesses in eyes with endophthalmitis, all without intraoperative complications. However, in the presence of retinal detachment, technically successful surgery is more difficult and the risk of complications is greater.

In eyes with retinal detachment, vitreous surgery can be used to cut vitreous bands and sheets causing traction detachment. Because of the surgical risks, we restrict this indication to eyes in which the macula is threatened or recently detached. Occasionally, vitrectomy may be needed to mobilize the flap of a giant retinal tear or to remove formed vitreous in order to permit injection of a gas bubble. We were not successful in achieving reattachment in eyes with retinal detachment complicated by progressive MVR. In general, vitreous surgery should be avoided in eyes with retinal detach-

TABLE 6

RESULTS OF VITREOUS SURGERY IN 51 DIABETIC EYES

Indications for Surgery	No. of Eyes	Vision Improved	Visual Acuity After Surgery		
			20/20–20/50	20/60–20/200	20/300–3/200
Vitreous hemorrhage	24	22	5	10	7
Traction detachment involving macula	6	1	—	—	1
Hemorrhage and detachment	21	8	—	—	8

TABLE 7

INTRAOPERATIVE COMPLICATIONS IN 100 EYES AT VITREOUS SURGERY

Complication	No. of Eyes
Retinal tear	37
Corneal damage with persistent edema	3
Incomplete lens removal	1
Uncontrollable hemorrhage	1
Endophthalmitis	1

ment if the situation can be successfully treated by conventional surgical means. In selected cases, however, vitreous surgery may be the procedure of choice or a helpful adjunct to conventional surgery.

The most significant intraoperative complications are retinal tears, uncontrollable intraocular hemorrhage, and endothelial damage causing permanent corneal clouding. Some corneal changes (stromal thickening and folds in Descemet's membrane) are invariably seen after vitrectomy in aphakic eyes. Significant corneal clouding is now an infrequent problem, although mild folds in Descemet's membrane may persist indefinitely in diabetic eyes. We recently decreased the incidence of corneal complications by avoiding removal of the epithelium and by removing the anterior lens capsule only toward the end of the operation (in eyes undergoing combined lensectomy and vitrectomy). This protects the corneal endothelium from the constant wash of the infusion solution.

Intraocular hemorrhage is only occasionally a problem during this surgery, even when proliferative tissue with patent blood vessels is cut. Generally, any bleeding quickly stops or can be tamponaded by elevating the intraocular pressure. The most difficult bleeding to control is from new vessels on the iris or from the greater arterial circle of the iris. One eye was lost because a faulty cutting-tip caused an iridodialysis, and the arterial bleeding could not be controlled despite penetrating diathermy to the ciliary body.

Retinal tears were a frequent intraoperative complication (37%). We recently decreased the incidence of dialyses near the sclerotomy site by enlarging the opening in uveal tissue with scissors prior to introducing the vitrectomy instrument tip. Retinal breaks represent a major threat to the eye. Every effort must be made to avoid causing retinal tears and to identify and treat any retinal break that may occur during surgery. Fortunately, these breaks can usually be successfully closed during the initial operation. Four eyes in this series developed retinal detachment that could not be successfully treated.

Vitreous surgery may result in postoperative complications such as phthisis bulbi and loss of light perception. Eyes at great risk to develop phthisis are those with preexisting retinal detachment complicated by MVR, and severely traumatized eyes with cyclitic membranes and hypotony. Also, certain eyes with advanced diabetic retinopathy (and its complications) may not tolerate the surgical trauma of vitrectomy. Generally, such eyes would be lost without a surgical procedure, but the high risk of complications makes them poor surgical candidates.

Rubeosis iridis also may develop after vitrectomy. We have the impression that rubeosis is a special risk in eyes with active proliferative retinopathy. It is possible that any vasoproliferative factor could more eas-

TABLE 8

POSTOPERATIVE OCULAR COMPLICATIONS IN 100 EYES AFTER VITREOUS SURGERY

No complications	53
Major complications	
Phthisis bulbi	9
Rubeosis and phthisis	8
Rubeosis	3
Major hemorrhage	5
Other complications	
Recurrent hemorrhage, small	7
Transient elevation intraocular pressure	6
Retinal detachment, successfully operated on	2
Persistent corneal edema	3
Cystoid macular edema	2
Hypotony	1
Macular pucker	1
	100

ily diffuse into the anterior segment after vitrectomy and lens removal.

Other common postoperative complications include recurrent vitreous hemorrhage and transient elevation of the intraocular pressure. Because the underlying vasoproliferative retinopathy is not affected by vitrectomy (other than relieving vitreoretinal traction), vitreous hemorrhage may recur after surgery. However, blood in the vitreous fluid in aphakic eyes has ready access to the anterior chamber outflow channels. This usually results in rapid clearing of recurrent hemorrhage. Temporary obstruction of the outflow channels by macrophages and erythrocyte cellular debris may result in hemolytic glaucoma.

The performance of pars plana vitrectomy is widespread and is valuable in selected cases. Although a larger group of cases and a longer follow-up period are necessary to assess fully the value of this procedure, our initial results are encouraging. However, this is a technically difficult operation that requires special skills and carries a high risk of complications. Improved results and a lower incidence of complications will probably result from further refinements in surgical technique and proper case selection.

Summary

We employed pars plana vitrectomy for several different indications in 100 eyes. In 51 eyes, the operation was performed for complications of proliferative diabetic retinopathy. Improved visual acuity was our only criterion of success, and this varied widely depending on the specific indication for surgery. Vision improved in all eight eyes undergoing anterior segment reconstruction and in none of three eyes with preoperative retinal detachment complicated by massive vitreous retraction. There was a high incidence of retinal tears complicating the operations in this series (37%). These retinal breaks could usually be closed at the time of the initial operation, and retinal detachment that could not be successfully managed developed in only four eyes.

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MANAGEMENT OF CATARACT IN PATIENTS UNDERGOING VITRECTOMY

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Since the first reports of vitreous body removal by automated means in 1971,[1,2] instrumentation has improved considerably.[3-9] Presently, vitreous body removal is done by the pars plana approach or by an open-sky vitrectomy[10]; the latter was recommended in the most severe cases of massive preretinal retraction.[8] The presence of a cataract complicates removal of vitreous hemorrhage via pars plana vitrectomy by preventing a clear view into the eye during surgery. Moreover, postoperative vision may be compromised by the cataract. In the past, presence of a cataract often dictated that vitrectomy would be performed as an open-sky technique, often complicated by postoperative corneal cloudiness.[11] We developed two surgical approaches for dealing with cataractous lenses in combination with opaque vitreous body. In both methods the vitreous body is removed through the pars plana, and during the same operation, the lens is removed either through the pars plana or through a separate corneoscleral limbus incision.

MATERIAL AND METHODS

The disposable lens fragmenter consists of two concentric tubes, similar to the vitrophage.[9] The outer tube has a diameter of 1.7 mm and is 35 mm long; the inner tube has a diameter of 1.5 mm (Figs. 1 and 2). The inner tube fits tightly inside the outer tube and extends through the end of the outer tube during downward pulsation. The linear oscillation of the inner tube is achieved by an air pressure system (Fig. 3) connected to the lens fragmenter by a tube. This system can be used either for the vitrophage or for the lens fragmenter. When the lens fragmenter is inserted inside the lens it works like a jackhammer to break the lens cortex and nucleus.

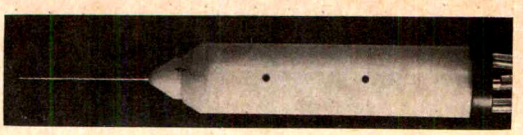


Fig. 1 (Peyman, Huamonte, and Goldberg). The disposable lens fragmenter.

Technique 1—This is a radical pars plana vitrectomy technique with removal of cataractous lens in the presence of moderate (1+ to 2+) nuclear sclerosis. Bridle sutures were passed around the four rectus muscles. We performed a partial limbal peritomy, usually at the inferior or superior temporal quadrant. Then we made a relaxing meridional incision in the middle of the fornix-based conjunctival flap to the fornix. We performed a 3-mm sclerotomy, 4.5 mm from the corneoscleral limbus and parallel to it (Fig. 4). Surface diathermy was applied to the edges of the sclerotomy to open it and to expose uveal tissue. Prolonged (2 to 3 seconds) low-intensity diathermy was then

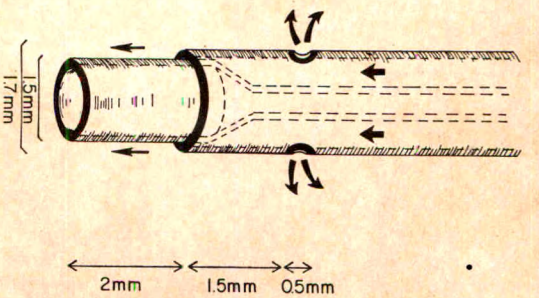


Fig. 2 (Peyman, Huamonte, and Goldberg). Dimensions of the lens fragmenter tip.

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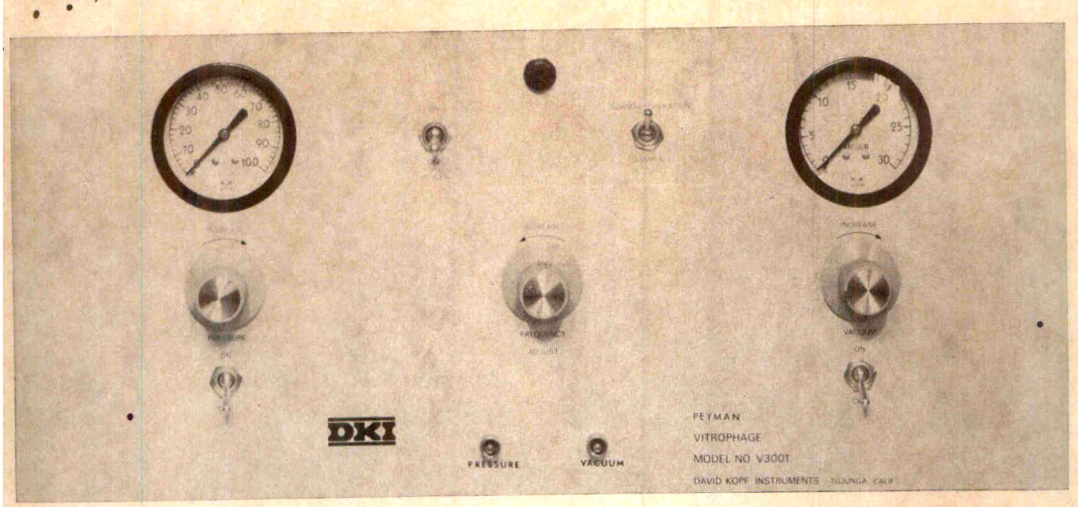


Fig. 3 (Peyman, Huamonte, and Goldberg). Front panel of the pulse generator for the lens fragmenter and vitrophage.

applied to the uveal vessels. A 5-0 Dacron mattress suture, passed through the sclerotomy, was looped out of the scleral incision, and the ends were tied loosely.

We introduced a Beaver knife with a No. 52S blade into the eye through the sclerotomy while the eye was stabilized with toothed forceps that grasped the sclerotomy lip, or with the bridle sutures. The knife, maneuvered forward, entered the lens at its equator (Fig. 5). With a gentle stab incision, we inserted the knife to the center of the lens. If the entire lens pushed away from the knife tip, it was too hard for this and subsequent steps; therefore, we removed the knife, temporarily closed the sclerotomy, and used technique 2. If the nucleus was soft enough, the knife penetrated without resistance. We removed the knife with a slicing motion to widen the tract for insertion of the lens fragmenter. The lens fragmenter was introduced into the lens, and the lens nucleus and cortex were fragmented by the hammering action of the lens fragmenter inner tubing (twice per second).

After removal of the lens fragmenter, we inserted the vitrophage into the lens, and aspirated, cut, and removed the fragmented lens material inside the lens capsule (Fig. 6). The lens capsule was not removed until we aspirated the cortex and the nucleus. Then we cut and removed the anterior and the posterior capsules. The lens capsule should be removed as completely as possible to prevent postoperative cataract formation.

We then performed a sector iridectomy in one or more meridians with the vitrophage. A vitrectomy followed the lentectomy and iridectomy procedures in the conventional manner,[1,2] by using a modified Goldmann posterior pole lens and an operating microscope (Figs. 7 and 8).

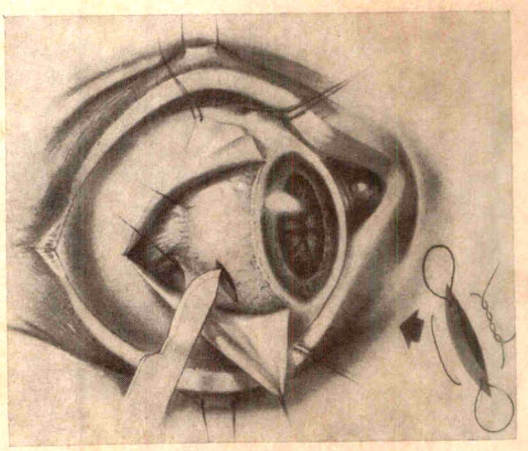


Fig. 4 (Peyman, Huamonte, and Goldberg). Fornix-based conjunctival flap at the temporal quadrant with relaxing incision at the mid-portion. Note the 3-mm sclerotomy, parallel to and 4.5 mm behind the corneoscleral limbus. Inset, Sclerotomy with mattress suture in place.

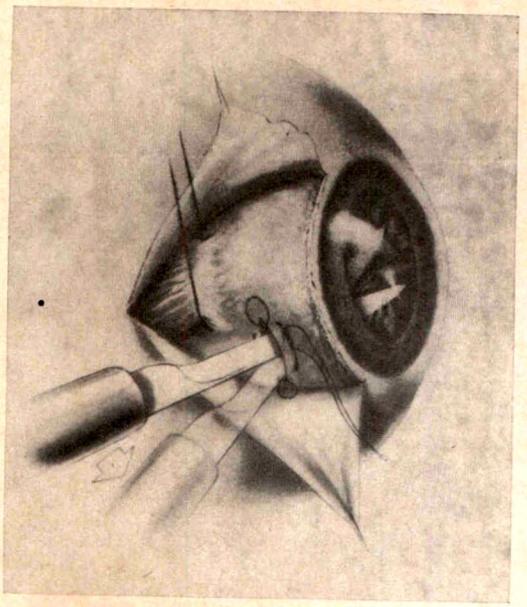


Fig. 5 (Peyman, Huamonte, and Goldberg). A Beaver blade was introduced through the pars plana sclerotomy into a cataractous lens by a gentle stab incision. Slicing motion widens the tract.

Technique 2—This is a radical pars plana vitrectomy technique with removal of the cataractous lens in the presence of intense nuclear sclerosis (3+ or more nuclear sclerosis and brunescent or mature cataract). We performed a conjunctival incision and prepared the sclerotomy as in technique 1. Then we inserted the Beaver knife into the eye through the sclerotomy; if the knife did not penetrate the hard cataractous lens or its nucleus (Fig. 9) but moved the nucleus away or dislocated the entire lens, the lens was too hard to be fragmented inside the eye. In that case, we removed the knife and closed the sclerotomy temporarily with the preplaced mattress suture.

Using a Bard-Parker No. 15 blade, we pierced the anterior chamber with an ab externo incision at the superior corneoscleral limbus. We enlarged the clear corneal incision by 150 degrees with corneal scissors. We placed a traction suture at the edge of the corneal flap at 12 o'clock. After performing a broad-sector iridectomy, we extracted the lens with a cryoprobe (Fig. 10), and closed the corneal incision with a 9-0 nylon running suture (Fig. 11).

We reopened the sclerotomy and performed the vitrectomy through the pars plana with the vitrophage, using a Goldmann macular lens and an operating microscope.

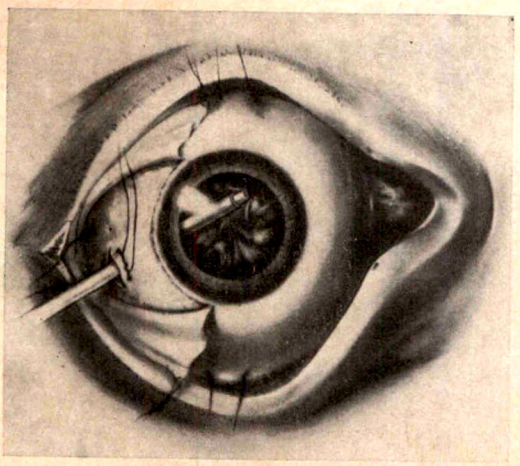


Fig. 6 (Peyman, Huamonte, and Goldberg). The lens fragmenter tip was inserted into the cataractous lens through the knife tract, and the lens was fragmented by the hammering action of the lens fragmenter.

Case reports

Ten consecutive patients underwent cataract extraction and vitrectomy by one of the two techniques (Table).

Case 2—A 52-year-old white diabetic man had had several vitreous hemorrhages in both eyes during the last two years. He had poor visual acuity

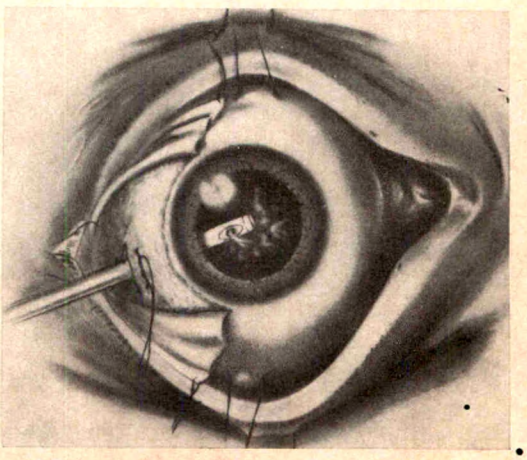


Fig. 7 (Peyman, Huamonte, and Goldberg). The vitrophage removes the fragmented lens material.

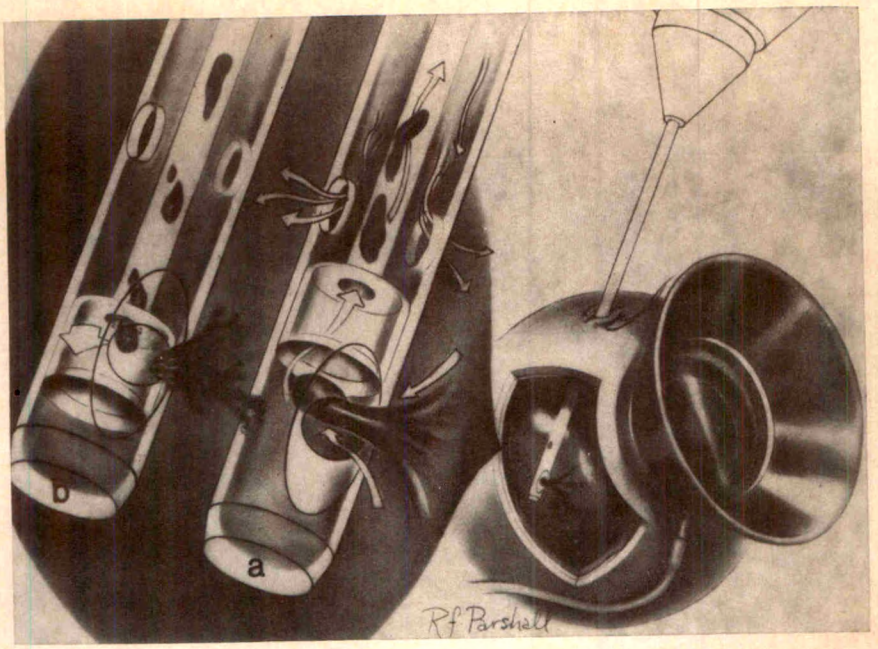


Fig. 8 (Peyman, Huamonte, and Goldberg). An "eye window" allows visualization of the vitrophage inside the vitreous cavity. Inset, Cutting action of the vitrophage. The fundus is visualized with a posterior fundus Goldmann lens and an operating microscope.

in the right eye because of long-standing retinal detachment. On March 18, 1974, visual acuity was light perception with poor projection in the left eye; he had 3+ posterior subcapsular cataracts in both eyes. On March 28, the patient underwent a vitrectomy and lentectomy through the pars plana (technique 1) in the left eye with no complications. The postoperative period was uneventful. Visual acuity was L.E.: hand motions, and ophthalmoscopic examination revealed a macular scar. Slit-lamp examination showed some lens remnants behind the dilated pupil. Intraocular pressure in the left eye was 15 mm Hg by applanation tonometry.

Case 6—A 70-year-old white diabetic woman complained of poor vision in both eyes for three years. On April 29, 1974, visual acuity was light perception with poor projection in both eyes, with 3+ nuclear sclerosis in the left eye. Vitreous hemorrhages obscured the fundus in both eyes. On May 27, we performed a lentectomy and vitrectomy in the left eye (technique 2). No complications occurred during surgery. Postoperatively, the eye had no more inflammation than after a routine cataract extraction. On June 19, visual acuity was L.E.: 20/100 with aphakic correction. The cornea was clear, the corneal wound was well healed, and the anterior chamber was deep with a 1+ flare. The fundus, clearly visible, showed fibrous tissue attached to the optic disk and hard exudates at the macular area. Intraocular pressure by applanation tonometry was 23 mm Hg in the left eye.

Discussion

In patients with extensive lens opacification, the lens must be removed prior to vitrectomy to allow an unobstructed view into

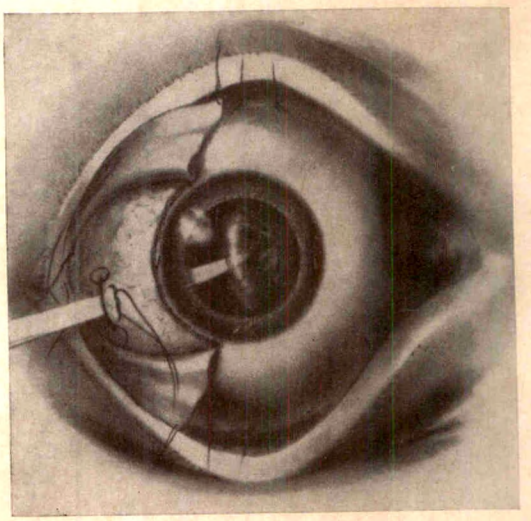


Fig. 9 (Peyman, Huamonte, and Goldberg). A Beaver knife introduced into the eye through a pars plana sclerotomy.

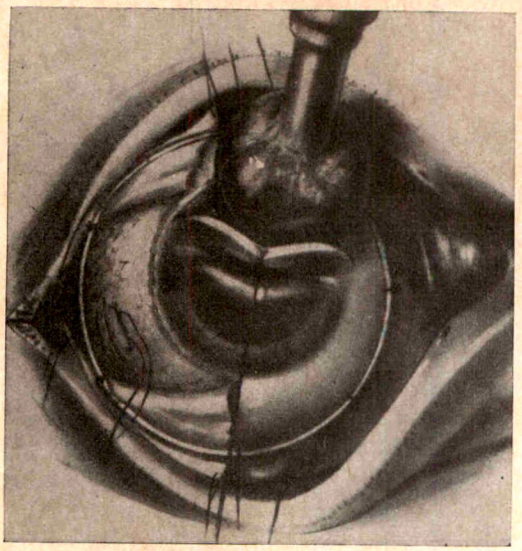


Fig. 10 (Peyman, Huamonte, and Goldberg). Cataract extraction with a cryoprobe through a 150-degree clear corneal incision.

the vitreous cavity and useful postoperative vision. However, when lens opacities are mild to moderate, the ophthalmologist may either do a vitrectomy first and perform a lens extraction later or vice versa, depending on whether the cataractous lens or the vitreous opacification is the major impediment to good vision.

We encountered varying degrees of lens opacity combined with vitreous hemorrhage. Diabetic patients, for example, whether they have massive vitreous hemorrhage or not, often have some degree of lens opacity. A Beaver knife easily penetrated lenses with posterior subcapsular cataract and a moderate amount (1+ to 2+) of nuclear sclerosis. The lens fragmenter was effective in softening the lens cortex and the lens nucleus. The vitrophage then efficiently removed the large pieces of lens nucleus and the cortex. In this technique, we left the posterior lens capsule intact until all other parts of the lens were removed, preventing loss of lens material into the vitreous body. We encountered no difficulty in cutting the lens capsule. After removal of the anterior lens capsule, the anterior chamber can collapse if extremely strong suction is applied. However, the chamber reforms immediately when the suction is released. Although early removal of the posterior capsule is not desirable because the lens material can be lost inside the vitreous body, the lens material can be removed from the vitreous cavity during the vitrectomy.

After removal of the lens, we performed a large-sector iridectomy or multiple excisional bites around the pupillary sphincter with the vitrophage to enlarge the pupil. Iris dialysis never resulted, perhaps because of the oscillating action of the vitrophage. In an oscillating system, the vitreous bands or the iris cannot wrap around the cutting blade as they can with rotary systems. Even in the presence of moderate rubeosis, iridectomies and sphincterectomies were not complicated by significant bleeding. On one occasion, we noted pulsatile bleeding immediately after excision of the iris specimen, but purposely raised the intraocular pressure for several seconds to halt the flow of blood.

In patients with 3+ or more nuclear sclerosis, the maneuver with the Beaver knife demonstrates whether the lens will dislocate prior to penetration of the knife into the nucleus or whether it is impenetrable. With cataract extraction described in technique 2, the cornea remains clear during and after

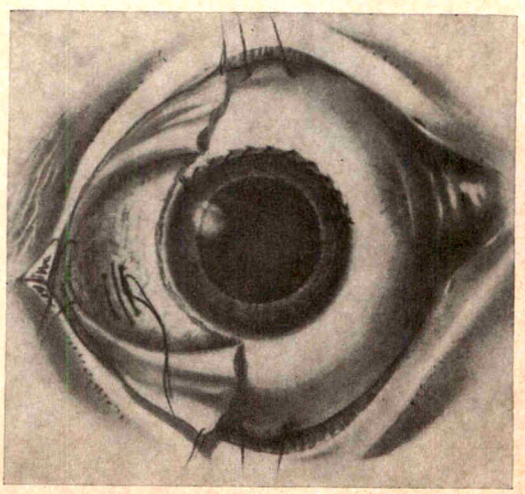


Fig. 11 (Peyman, Huamonte, and Goldberg). Corneal incision closed with a 9-0 nylon running suture. Iridectomy can be done before cataract extraction (standard fashion) or with the vitrophage.

TABLE

SUMMARY OF PATIENT DATA*

Case No., Sex, Age (yr)	Underlying Disease	Operated Eye	Type of Cataract	Lentectomy Technique	Visual Acuity		Postoperative Intraocular Pressure,† mm Hg	Immediate Postoperative Appearance
					Preoperative	Postoperative		
1, M, 22	Trauma	LE	2+PSC	1	HM	20/25	15	1+ flare in anterior chamber
2, M, 52	Diabetes	LE	3+PSC	1	LP	HM	15	Lens remnants behind iris; 1+ flare in anterior chamber
3, F, 49	Systemic hypertension	LE	2+PSC 1+NS	1	CF	20/30	18	Lens remnants behind iris; 1+ flare in anterior chamber
4, M, 38	Diabetes	LE	2+PSC 1+NS	1	HM	HM	10	Capsule remnants behind the iris
5, F, 57	Diabetes	RE	3+PSC 2+NS	1	HM	20/400	24	Capsule remnants behind iris; 2+ to 3+ flare in anterior chamber
6, F, 70	Diabetes	LE	3+NS 1+PSC	2	LP	20/100	23	1+ flare in anterior chamber
7, F, 54	Diabetes	RE	4+NS 2+PSC	2	HM	20/400	19‡	1+ flare in anterior chamber; elevated IOP after vitrectomy
8, M, 53	Diabetes	LE	3+NS 3+PSC	2	LP	HM	24	1+ flare in anterior chamber
9, M, 70	Diabetes	LE	2+ to 3+ NS 2+PSC	2	LP	20/200	26	1+ flare in anterior chamber; 1+ Descemet fold
10, M, 75	Diabetes	RE	3+NS	2	20/800	20/40	22	1+ flare and 1+ cells in anterior chamber

* PSC signifies posterior subcapsular cataract; NS, nuclear sclerosis; HM, hand motions; LP, light perception; and CF, counting fingers.

† Preoperative intraocular pressures (IOP) were within normal limits.

‡ With 250 mg of acetazolamide daily.

the operation. (None of our patients developed postoperative corneal cloudiness.) In both techniques, the amount of postoperative inflammation was mild. The corneal sutures may remain for a long period of time; however, sutures may be removed six weeks after the operation. We encountered no wound dehiscence either during the vitrectomy procedure or postoperatively.

Although lentectomy through the pars plana has been described previously by Machemer,[12] he did not use a lens fragmenter to soften the lens prior to its removal.

We believe that surgical removal of hard lenses through the pars plana can be tedious and hazardous, as loss of the lens or the nucleus can complicate the procedure considerably. It may prolong the operating time; also, manipulation of the dislocated lens inside the vitreous body increases the risk of mechanical injury to the retina, or may cause damage to the corneal endothelium if the lens dislocates into the anterior chamber. With the described techniques, cataractous lenses can be easily removed without complication, and vitrectomy can be done in the same operative session.

SUMMARY

We developed two techniques to combine vitrectomy with cataract extraction. In technique 1, we used the lens fragmenter to break up cataractous lenses with 1+ to 2+ nuclear sclerosis. The vitrophage removed the lens and opaque vitreous body through a single pars plana incision. In technique 2, if the knife did not penetrate the nucleus (in the presence of 3+ or more nuclear sclerosis), we removed the lens through a corneal incision and immediately performed a vitrectomy with a vitrophage through the pars plana. In ten consecutive patients, we used these tech-

niques successfully to remove cataractous lenses in patients undergoing vitrectomy for vitreous hemorrhage.

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INTRAVITREAL HEMORRHAGE ASSOCIATED WITH RAPID INCREASE IN INTRACRANIAL PRESSURE (TERSON'S SYNDROME)

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The occurrence of retinal, preretinal, or subhyaloid hemorrhages in association with bleeding in the subarachnoid space is not uncommon. Frank intravitreal hemorrhage under these circumstances is more unusual and has been called Terson's syndrome.[1] This unusual circumstance occurred in three patients, resulting in complete recovery of vision in one, fibrous reaction in two, and a similar mechanism in a fourth patient.

CASE REPORTS

Case 1—A 52-year-old woman with known hypertension had been receiving hydrochlorothiazide for three years. She noted the onset of bitemporal headaches followed almost immediately by decreased vision in the right eye. On admission to another hospital she manifested marked nuchal rigidity and a preretinal hemorrhage. A spinal puncture showed an opening pressure of 270 mm H_2O with a grossly bloody cerebrospinal fluid. She remained conscious and cooperative. The only neurologic sign was deep tendon reflex hyperactivity on the left side. Blood pressure ranged from 160/100 to 130/86 mm Hg. Bilateral carotid and left brachial angiography failed to demonstrate the presence of an intracranial aneurysm. Treatment of the hypertension and bedrest resolved the clinical syndrome related to the subarachnoid hemorrhage and the patient was discharged six weeks after the initial episode. At ophthalmologic consultation one week later, visual acuity was R.E.: hand motions, and L.E.: 20/20. The external appearance and anterior segments of both eyes were unremarkable. The pupillary responses were active directly and consensually. However, we obtained no red reflex on ophthalmoscopic examination on the right side by means of the highest intensity of direct and indirect ophthalmoscopes. The media of the left eye were clear and the retinal arterioles were markedly attenuated with considerable arteriovenous compression. Some fan-shaped hemorrhages were visible in an area 2 disk diameters inferonasal to the disk. The disk itself showed no signs of edema or significant venous congestion. The intraocular pressures were normal.

Four months later the vitreous debris was nearly resorbed and visual acuity was correctable to 20/40 (R.E.). No abnormalities of the disk or retinal vessels were noted. When seen four years later, the patient was completely symptom-free. Blood pressure was well controlled on 250 mg of chlorothiazside and 0.1 mg of reserpine daily. Visual acuity was correctable to 20/20 in each eye. The media were clear. The optic disks were normal. The right macula showed some pigmentary dispersion while the retinal arterioles appeared normal (Fig. 1).

Case 2—A 34-year-old woman was admitted with complaints of severe bifrontal headaches, bilateral loss of vision, and weakness of the left lower extremity of approximately three months' duration. She was a known hypertensive, but was not receiving medication. She was alert and oriented with a blood pressure of 107/68 mm Hg and a supple neck.

Ophthalmologic examination revealed a nearly complete left internal and external third cranial nerve palsy with blepharoptosis. The left pupil was briskly reactive. Visual acuity was R.E.: light perception, and L.E.: finger counting in the temporal field. Massive vitreous hemorrhages obscured visualization of the fundi bilaterally. The remainder of the neurologic examination was unremarkable. Bilateral carotid angiograms demonstrated an aneurysm rising from the bifurcation of each posterior communicating artery. Another small aneurysm was visible arising from the right anterior communicating artery. Subsequently, a right frontotemporal craniotomy and clipping of the right posterior communicating artery aneurysm were performed. Four months after the initial hemorrhage, visual acuity was R.E.: 4/400, and L.E.: counting fingers. There was early resolution of the vitreous hemorrhages, but organized vitreous strands were apparent. The patient was readmitted for clipping of the left posterior communicating artery aneurysm.

Case 3—A 38-year-old woman had a history of multiple cerebral aneurysms and subarachnoid hemorrhages seven years previously. In the three years after symptom development, the patient underwent a right carotid ligation, left internal carotid aneurysm ligation, and craniotomy for a suspected basilar artery aneurysm that was not uncovered. Acute hydrocephalus was treated by ventriculopleural shunting.

She was first seen at the Neuropsychiatric Institute March 9, 1970, for a shunt revision. She had bilateral sixth nerve palsies. Visual acuity was R.E.: 20/70, and L.E.: 20/200. The view of both

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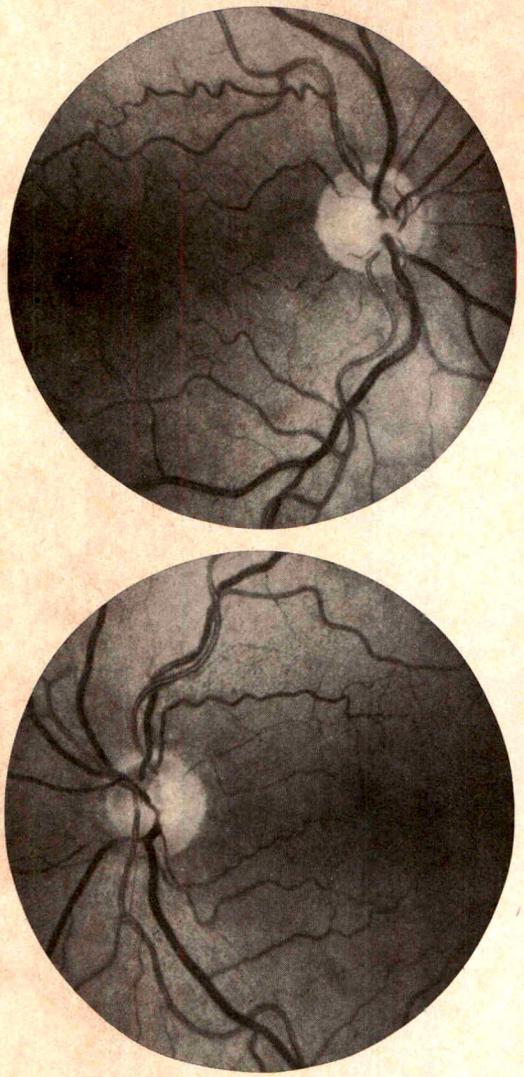


Fig. 1 (Khan and Frenkel). Case 1. Normal right (top) and left (bottom) posterior poles four years after right intravitreal hemorrhage associated with subarachnoid bleeding. Visual acuity was 20/20 in both eyes.

fundi was obscured by vitreous opacification and hemorrhage. The visual fields were grossly normal.

On readmission May 3, 1971, for another shunt revision, the vitreous cavity was still cloudy and old retinal hemorrhages were apparent bilaterally. Visual acuity was not recorded. Bilateral sixth nerve palsies were again observed.

When we examined her on June 10, 1974, for increasing lethargy, we noted a left spastic hemiparesis with contractures at elbow and ankle joints. Hyperreflexia on the left side and extensor plantar responses were noted, prompting a further shunt revision.

On ocular examination, abduction and adduction were impaired bilaterally. We observed debris and detachments of the vitreous with fibrous organization and prepapillary vitreal gliosis in both eyes (Fig. 2). Visual acuity was R.E.: 20/50, and L.E.: 20/60.

Case 4—A 22-year-old man from a state penal institution had complaints of headache and blurred vision. He had been assaulted by several inmates three weeks previously and had been unconscious for an unknown period of time; he presumably was strangled and knocked on the head. Vital signs were normal. He appeared slowly responsive but well oriented. No motor or sensory loss was

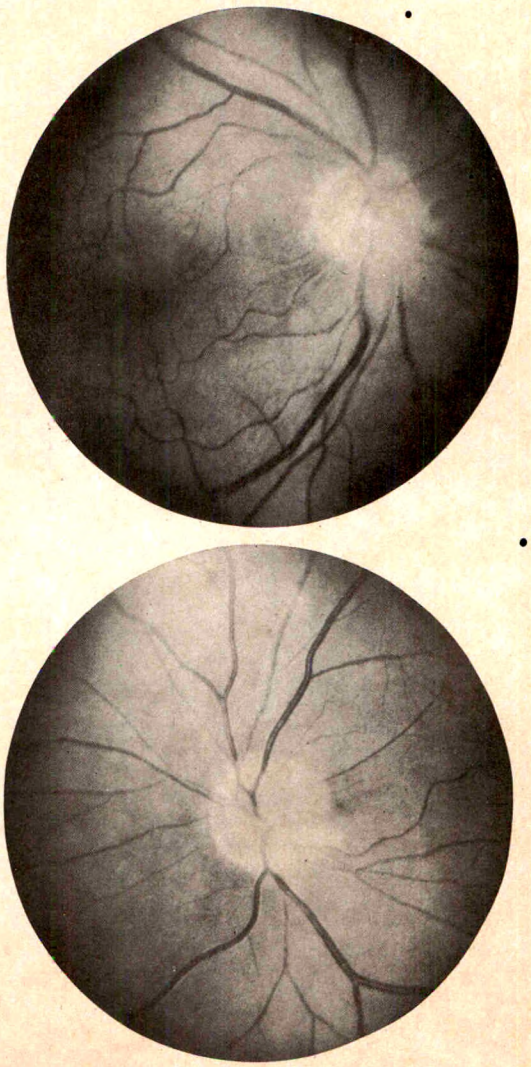


Fig. 2 (Khan and Frenkel). Case 3. Right (top) and left (bottom) posterior poles seven years after bilateral intravitreal bleeding with mild gliosis of both optic nerve heads. Visual acuity was R.E.: 20/50, and L.E.: 20/60.

noted, yet bilateral Babinski's signs were present. Ocular motility was full with equal and reactive pupils. There was massive bilateral papilledema with hemorrhages around the disk on initial evaluation. An echoencephalogram revealed a 5-mm left to right shift. Skull x-ray films were negative. A provisional diagnosis of chronic subdural hematoma was made, but bilateral burr holes failed to reveal subdural blood and a right brachial angiogram was normal.

Neuro-ophthalmologic consultation two days later showed visual acuity of 20/30 in both eyes. The eyelids and ocular movements were intact. The pupils were equal and reactive. There was edema of the nerve heads with spoke-like peripapillary hemorrhages. Fluffy exudates, hemorrhages, and fibrin material were evident in the vitreous cavity (Fig. 3).

We thought the vitreous hemorrhages were caused by rapid increase in intracranial pressure due to trauma, with strangulation or thoracic compression acutely increasing the intravenous pressure.

Three months later, visual acuity was R.E.: 20/20, and L.E.: 20/25. The vitreous cavity and fundi were completely normal.

Discussion

The first patient (Case 1) is particularly interesting because of two factors: (1) most cases of Terson's syndrome are associated with rupture of aneurysms of the carotid or its branches or aneurysms of the anterior communicating artery, and (2) few described patients experienced complete recovery of vision following a massive intravitreal hemorrhage. Our patient did not have a demonstrable intracranial aneurysm and has been symptom-free for a follow-up of five years. Visual acuity recovered to 20/20 without evidence of hypertensive retinopathy or significant macular disturbance.

Two patients (Cases 2 and 3) had Terson's syndrome with intracranial aneurysms and subarachnoid hemorrhages associated with vitreous bleeding. Both cases resulted in fibrous organization and a decrease in visual acuity. The fourth case likely resulted from a superior vena caval obstruction mechanism caused by throttling or compression of the thorax and abdomen. This caused a sudden increase in intracranial pressure resulting in papilledema and vitreous hemorrhages. Subsequent follow-up four months after the assault revealed the vitreous body and fundi to be completely normal.

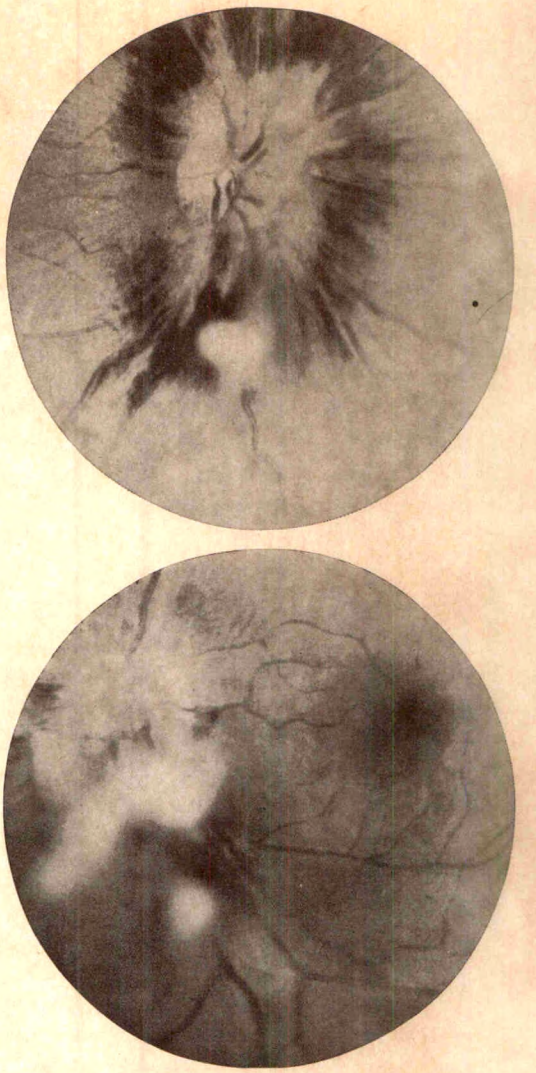


Fig. 3 (Khan and Frenkel). Case 4. Bilateral peripapillary hemorrhage and intravitreal debris three weeks after strangulation. Visual acuity was 20/30 in both eyes.

Recently, Fahmy[2] found evidence of intraocular hemorrhage in 50 of 154 (32.4%) patients with subarachnoid bleeding; 21 cases were bilateral while nine had vitreous hemorrhage. In four additional cases papilledema alone was present. The severity of the hemorrhage ranged from streak or flame-shaped papillary, peripapillary, and peripheral hemorrhages to large preretinal or vitreous blood

accumulation, in a distribution similar to that reported by Timberlake and Kubik.[3] The retinal hemorrhages may occur almost simultaneously with the subarachnoid bleeding or may be delayed, representing late rupture of retinal vessels. Walsh and Hoyt[4] and Fahmy[2] suggested that return to normal vision is rare after vitreous hemorrhage. However, Vanderlinden and Chisholm[5] noted total recovery in four of six cases. Visual acuity loss may be due to persistent opacities or fibroblastic proliferation within the vitreous that could cause retinal detachment. Other causes for visual acuity loss include macular changes related to the hypertensive vasculopathy or presumed toxic effects of the blood pigments on the retina.

The mechanism for intraocular hemorrhages associated with subarachnoid bleeding has been the subject of some controversy. Most authorities agree that there is no communication between the subarachnoid space and the vitreous cavity in normal eyes. The dural sheath accompanies the optic nerve to the lamina cribrosa where it merges with the pia mater into the sclera. Dissection of blood from the subarachnoid space through the lamina cribrosa into the eye is unlikely, although early observers suggested such a mechanism.[6-8] Examination of the fine structure of the optic papilla by electron microscopy also failed to reveal communication between the subarachnoid space and the vitreous cavity in the normal eye.[9]

However, in considering the pathogenesis of subretinal edema in association with pits of the optic nerve, Gass[10] suggested that, in this unusual instance, there may be a communication between these two spaces, and that subretinal fluid represents an accumulation of cerebrospinal fluid. Nerves with optic pits are unilateral and are enlarged in relation to the fellow eye by a factor or two. Optic pits are claimed to be atypical colobomas, related in some way to malclosure of the fetal fissure. According to Ferry,[11] the lamina cribrosa is absent and sometimes the pits may reach into the subarachnoid space where they are cystic in form. According to M. J. Hogan (personal communication, Nov. 29, 1972), there is no communication into the eye under normal circumstances. L. E. Zimmerman (personal communication, Oct. 18, 1972) agrees with this formulation, but thinks that in the case of a congenital pit there could be an anatomic malformation that permits the seepage of subarachnoid fluid into the subretinal space.

Another exception to the separation of subarachnoid from the vitreous space might occur in the unusual circumstance of an evulsion of the optic nerve head following trauma. During the acute phase of one such case,[12] it appeared that the optic nerve was dislocated posteriorly. The papilla appeared indented into a pit that seemed to contain a fluid distinct from the vitreous fluid when observed by a Goldmann lens.

Ocular hemorrhage associated with subarachnoid bleeding likely results from a sudden and massive increase in intravenous pressure secondary to the intracranial hypertension resulting from the bleeding. In internal hydrocephalus, there usually is a gradual increase in cerebrospinal fluid pressure. This is transmitted through the subarachnoid space with a slow increase in the central retinal venous pressure. The retinal venous channels may gradually dilate and compensate for the embarrassed circulation, causing a relatively modest papilledema. A sudden increase in intracranial pressure does not allow for this gradual compensation and causes an acute venous engorgement. When the rate of intravenous pressure increase is extremely rapid, small papillary capillaries or venules rupture, causing significant bleeding. These may penetrate a disturbed posterior vitreous face or conceivably dissect into Cloquet's canal, resulting in dispersion of blood within the vitreous body. In contrast, in some cases of chronic papilledema such as pseudotumor cerebri, hemorrhages may be slight or nonexistent and the central retinal vein may even

be pulsatile, implying an equilibrium between the intravenous and intracranial pressures. When a sudden increase in intravenous pressure occurs, as in crush injuries of the abdomen or thorax (Case 4), and after epileptic seizures, posterior pole hemorrhages may be seen. Under these circumstances compression of the central retinal vein occurs where it traverses the intervaginal spaces. The resulting back pressure is sufficient to cause rupture of retinal veins and capillaries. Greear[13] credits Uhthoff[14] as the first to question the theory of direct extension from subarachnoid space into the retina. Greear[13] reported a case in which histopathologic examination revealed dilatation of the central retinal vein intraocularly, with collapse of the vein in the subarachnoid space of the optic nerve.

Riddoch and Goulden[15] suggested that there is retinal vein congestion because of compression of the central retinal vein by hemorrhage in the intervaginal space, accompanied by traction on the vein caused by separation of dural and pial sheaths. Drews and Minckler[16] noted that the retinal hemorrhages may not be contiguous with the optic disk, so blood could not have forced its way through the lamina cribrosa. Other authors[17-19] pointed out that the stronger and less compressible arterial wall is less affected by the pressure and, hence, arterial flow is not decreased. Tureen[20] also noted that pontine hemorrhage without subarachnoid extension causes intraocular hemorrhage. Hemorrhages that lie so far from each other can only be explained on the basis of a suddenly increased intracranial pressure. This pressure, transmitted rapidly to the optic nerve sheaths, produces a rapid venous stasis. Castren[21] emphasized the rapidity of the increased intracranial pressure as an essential factor that causes rupture of presumably healthy vessels in the eyes of young people. Miller and Cuttino[22] advanced a third possible mechanism for intraocular hemorrhages related to compression of the choroidal anastomotic channels. While others theorized obstruction to the central retinal vein in the intervaginal space only, these authors[22] believed that the choroidal anastomoses would undergo compensatory distention and prevent rupture of retinal veins (Fig. 4). Hence, the same pressure exerted on the central retinal vein in the subarachnoid space, as it leaves the optic nerve, is also transmitted directly against the lamina cribrosa, resulting in compression of the choroidal anastomoses. Both mechanisms, working simultaneously, leave no avenue for the return of venous blood from the retina.

The mechanism of Terson's syndrome in Case 4 is similar to one described by Walsh and Hoyt[4] who cited the occurrence of retinal and vitreous hemorrhages in a criminal assault and strangulation case. There was intense venous congestion of the brain and face with a dramatic increase of intracranial pressure. An almost similar mechanism can be cited in cases of retinal hemorrhages in neonates. Obstetric trauma and the complicated passage of the infant through the birth canal or loops of cord around the neck could result in an increase in intracranial pressure sufficient to cause rupture of venules and capillaries. Giles[25] suggested that the degree of head control and rapidity of release of intracranial pressure at birth play an important role. He implicated this high pressure gradient as the main cause of rupture of blood vessels.

There is considerable variation in the time interval between the onset of subarachnoid hemorrhage and the appearance of ocular hemorrhage. In his study of four cases, Tureen[20] noted that the shortest interval within which fundic changes appeared after onset of cerebral symptoms was two hours. Walsh and Hoyt[4] stated that fulminating hemorrhagic papilledema can be established in five to eight hours. They observed two patients with vitreous hemorrhage as a delayed phenomenon, with extension of a preretinal hemorrhage into the vitreous cavity five to seven days later. The internal limiting mem-

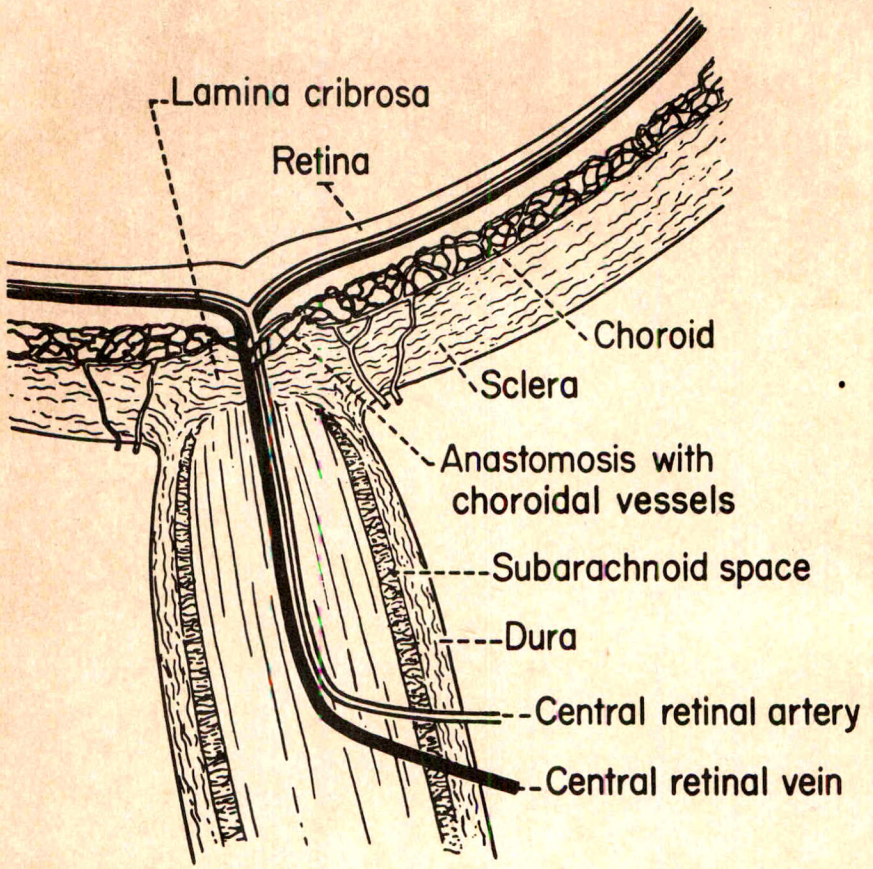


Fig. 4 (Khan and Frenkel). The relationship between the central retinal vein, choroidal circulation, and subarachnoid space (adapted from Last[23] and Hayreh[24]).

brane of the retina is apparently able to contain most preretinal hemorrhages, and only occasionally does the blood pass forward into the vitreous cavity, resulting in Terson's syndrome.

Resolution of vitreous hemorrhage varies. One patient (Case 1) showed remarkable improvement and a subsequent visual acuity of 20/20 with a vitreous body free of cells, observed by a Goldmann lens. Walsh and Hoyt[4] also observed clearing of massive intraocular hemorrhages in one case with recovery of normal vision more than one year later, while others[5] noted improvement in 18 to 24 months. However, it is not always possible to improve visual acuity by conservative methods. Castren[21] described transplantation of the vitreous from a cadaver or replacement of the opaque vitreous by hyaluronic acid. The recent development of vitrectomy[26,27] may tempt the ophthalmologist to apply this procedure in treating Terson's syndrome. Since clearing of the hemorrhage occurs in most instances within a year, earlier vitrectomy should be reserved for massive bilateral bleeding with reduction of vision limiting the patient's activity. This situation (Case 2) may dictate a relatively premature surgical intervention.

Summary

Four patients manifested Terson's syndrome in association with increased intracranial pressure. Three patients had subarachnoid hemorrhages, while the fourth suffered strangulation. Vitreous hemorrhage

probably is related to the rapid increase in intracranial pressure with compression of the central retinal vein and its choroidal anastamotic channels.

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COMPLICATIONS OF ACUTE POSTERIOR VITREOUS DETACHMENT

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The sudden appearance of flashing lights or vitreous floaters, or both, are symptoms frequently associated with acute posterior vitreous detachment (PVD). This condition is clinically important since it may be indicative of more serious vitreoretinal pathologic findings. The complications of acute PVD are retinal break formation, vitreous and retinal hemorrhage, and cystoid maculopathy.[1-4]

Entoptic phenomena associated with acute PVD are usually due to concurrent vitreous hemorrhage or to the shadows cast onto the retina by the detached hyaloid attachment to the optic disk. Photopsia is probably caused by the disruption of vitreoretinal adhesions, or by the collapsed vitreous body bumping into the retina during eye movements.[5]

I tried to determine the incidence and clinical features of the complications associated with acute PVD.

PATIENTS AND METHODS

The clinical records of all new patients referred to the retinal clinic between January 1968 and July 1974 were screened (1,103 patients). Those who presented with sudden photopsia or entoptic phenomena, or both, were analyzed.

Several categories of patients were arbitrarily excluded from the study: those with a history of migraine; those with known preexisting ocular disease; those with a history of significant ocular trauma; those whose eyes did not have sufficiently clear media to permit adequate visualization of the fundi; and those who had a retinal detachment on initial examination.

Of 201 patients who fulfilled the necessary criteria, 82 were men and 119 were women; 52.7% reported only the appearance of floating opacities, 9.5% complained of light flashes only, and 37.8% presented with both flashes and floaters. Ten patients presented with acute symptoms bilaterally.

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RESULTS

One hundred fifty patients (75%) had PVD. Of the 51 who showed no evidence of PVD, 20 (10%) had vitreous hemorrhage while 31 (15%) experienced symptoms but no known causes (Table).

Retinal breaks—In the 150 patients with acute PVD, we found 89 retinal breaks in 76 eyes of 69 patients (46%). Of the 76 eyes with symptomatic retinal breaks, 40 eyes (52.6%) were myopic, and the degree of myopia exceeded −10 diopters in seven eyes. Seven patients had retinal breaks in asymptomatic fellow eyes. Of the 89 retinal breaks, 53 were U-shaped and 36 were round; 12 breaks occurred in areas of lattice degeneration. Vitreous hemorrhage was present in 63.8% of cases with PVD and retinal breaks; the incidence of vitreous

TABLE

SURVEY OF 150 PATIENTS WITH ACUTE POSTERIOR VITREOUS DETACHMENT

Data	No. of Patients	%
Men	57	38.0
Women	93	62.0
Complications	89	59.3
Retinal breaks	69	46.0
With vitreous hemorrhage	(44)	(63.8)
Without vitreous hemorrhage	(25)	(36.2)
Myopes	(40 eyes)	(52.6)
No retinal breaks	20	13.3
Vitreous hemorrhage	(18)	(12.0)
Retinal hemorrhage	(2)	(1.3)

hemorrhage in eyes with U-shaped tears (80%) was significantly higher than the incidence of vitreous hemorrhage in eyes without U-shaped tears (37.5%). The majority of breaks were situated near the equator. Seventy percent of breaks were situated in the upper temporal quadrant, 14% in the lower temporal quadrant, 10% in the upper nasal quadrant, and 6% in the lower nasal quadrant. The complaint of light flashes appeared to be unrelated to the incidence of retinal breaks.

Vitreous hemorrhage—Vitreous hemorrhage without retinal breaks was present in 18 patients with PVD.

Retinal hemorrhage—Two patients had peripheral retinal hemorrhages without either retinal breaks or vitreous hemorrhage.

Sixty-one patients (40.7%) had uncomplicated PVD that occurred bilaterally in eight cases.

Discussion

The majority of patients in this study who presented with the sudden appearance of entoptic phenomena or photopsia, or both, had acute PVD.

Acute PVD results from the fibrillary portion of the internal limiting membrane splitting into two layers.[6] A defect in the inner layer allows the abrupt passage of liquefied vitreous humor into the newly formed retrovitreal space. As a result, the two layers become separated; the outer layer remains attached to the retina, but the inner layer becomes detached as far as the posterior expansion of the vitreous base. The main mass of solid vitreous collapses and sinks inferiorly. After PVD, the retina is no longer protected by the stable vitreous cortex, and vitreous traction can now directly affect the retina. The incidence of complications of acute PVD seems to depend on the extent and strength of pre-existing paravascular and vascular vitreoretinal attachments. If the adhesions are strong the retina may be torn or retinal blood vessels avulsed.[7]

The incidence of retinal breaks in previous reports on acute PVD complications varied from 11[2] to 15.1%,[1] and the incidence of vitreous hemorrhage in the absence of detectable retinal breaks varied between 5[2,3] and 6%.[1] The incidence of retinal breaks associated with acute PVD (46%) and the 12% incidence of vitreous hemorrhage in the absence of breaks is higher here than in other studies. This discrepancy is probably due to the fact that the patients included in this study were a preselected group, examined by other ophthalmologists, and only patients with suspicious vitreoretinal pathologic findings were referred here for further examination.

The reported incidence of vitreous hemorrhage in eyes with breaks and acute PVD varied from 100[2] to 64%.[3] My findings (63.8%) agree with those of Tasman (64%).[3] The finding that the symptom of light flashes appears to be unrelated to the incidence of retinal breaks agrees with past observations.[1-3]

In this series 70% of retinal breaks occurred in the upper temporal quadrant. This correlated well with the distribution of retinal breaks in patients with retinal detachment,[8,9] but is in contrast with the predominantly inferior distribution of breaks in eyes examined at autopsy,[10] and in a clinical study of asymptomatic retinal breaks in presumably normal patients.[11] In most cases, the retinal breaks that occur in association with acute PVD are dangerous according to accepted criteria[12,13]: fresh, U-shaped, situated near the equator, in the upper part of the eye, and associated with vitreous hemorrhage. In most cases, retinal breaks occurred in normal-looking retinas, unassociated with lattice degeneration; in several eyes, acute PVD occurred in the presence of lattice degeneration but retinal breaks did not develop.

Tasman[3] found that retinal hemorrhages along the posterior border of the vitreous base may be a sign of vitreous traction and of incipient retinal break formation. Four

of our patients had peripheral retinal hemorrhages in association with acute PVD. A retinal break developed at the site of the hemorrhage in one patient; two months later another patient developed a retinal break but at a different site; and two others did not develop breaks and the hemorrhages cleared spontaneously after several weeks. In another patient, a retinal break was found more than a year after the initial episode of acute PVD. The formation of delayed retinal breaks probably is the result of continued traction along pre-existing vitreoretinal attachments that are usually along blood vessels or along abnormal insertions of the vitreous body to the retina, just posterior to the vitreous base.[14,15] For this reason, a patient who presents with acute PVD must be observed for at least several months in anticipation of possible late complications.

Summary

Of 201 patients whose presenting symptoms were acute entoptic phenomena or photopsia, or both, 150 patients had posterior vitreous detachment; 69 patients (46%) had retinal breaks; 18 (12%) had a vitreous hemorrhage without detectable retinal breaks; and two (1.3%) had peripheral retinal hemorrhages without retinal breaks or vitreous hemorrhage. Retinal breaks that occur in eyes in conjunction with acute posterior vitreous detachment are potentially dangerous and there is a possibility of delayed break formation.

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COAGULATION AND PLATELET ADHESION-INDUCING FACTOR IN THE ENDOTHELIUM OF THE RETINAL VESSELS

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Blood coagulation factor VIII (antihemophilic factor A or AHF) is a plasma protein involved in the formation of plasma thromboplastin, the first step of blood coagulation. The occurrence of a defective AHF protein causes a hereditary hemorrhagic disorder known as hemophilia A. The AHF protein in normal plasma has another activity, the so-called von Willebrand Factor (vWF) activity. It may thus be called AHF-vWF protein. vWF is necessary for platelet adhesion[1] and its deficiency is accompanied by a disorder of primary hemostasis known as von Willebrand's disease, characterized by prolonged bleeding time, reduced platelet adhesiveness, and decreased factor VIII activity.

The endothelium of the retinal vessels contains a powerful fibrinolytic activator.[2] In the present study, we showed that the intima of the retinal vessels also contains AHF-vWF protein.

MATERIAL AND METHOD

Human eyes were obtained at autopsy from patients who died from diseases not involving the eyes. The interval between death and autopsy never exceeded 12 hours. Human fetal eyes were collected at abortion. The eyes were quickly frozen in liquefied petroleum gas refrigerated by liquid nitrogen and immediately processed or stored in sealed plastic bags at −60°C.

Frozen sections, 6 μ thick, were placed on glass slides, washed in saline, air dried, fixed in absolute methanol, and then rewashed twice in phosphate-buffered saline, pH 7.8. Fluorescein isothiocyanate (FITC)-conjugated antiserum was dropped onto the sections, and the sections were incubated for one hour in a moist chamber. The sections were then washed four times in phosphate-buffered saline, mounted in glycerol, and sealed with paraffin.

We obtained the antiserum to AHF-vWF.[3] The IgG fraction of the antiserum was prepared by means of the Steinbuch and Audran method.[4] IgG was dissolved in 0.02M tris-(hydroxymethyl) hydrochloride, pH 7.4, and 0.15M sodium chloride, dialyzed against saline, and diluted to a concentration of 20 mg/ml. We performed the conjugation by means of the Holborow and Johnson method,[5] using an FITC isomer (I). The conjugation mixture was dialyzed against 0.01M phosphate buffer, pH 7.2, and chromatographed on DEAE-cellulose (Whatman DE 52) with stepwise elution, using 0.1 to 0.3M phosphate buffers, pH 7.2. The protein eluted with 0.2M phosphate buffer was used. The fluorescein/protein molar ratio was 2.0.

Fluorescence microscopy epi-illumination[6] with narrow band excitation of FITC was used. The light source was an HBO 100 mercury lamp, the primary filters were GG 475, 2xKP 490, TK 490, and the secondary filter Al 525.

Frozen sections of the retinal vessels were also examined by a modification[2] of the fibrin slide technique[7] for the microscopic localization of fibrinolytic activity.

RESULTS

The intima of the retinal vessels both from fetal and adult eyes regularly showed FITC fluorescence (Figs. 1 and 2). The intraocular branches of these vessels were active (Fig. 3). FITC fluorescence was seen occasionally at the site of the choroid, while

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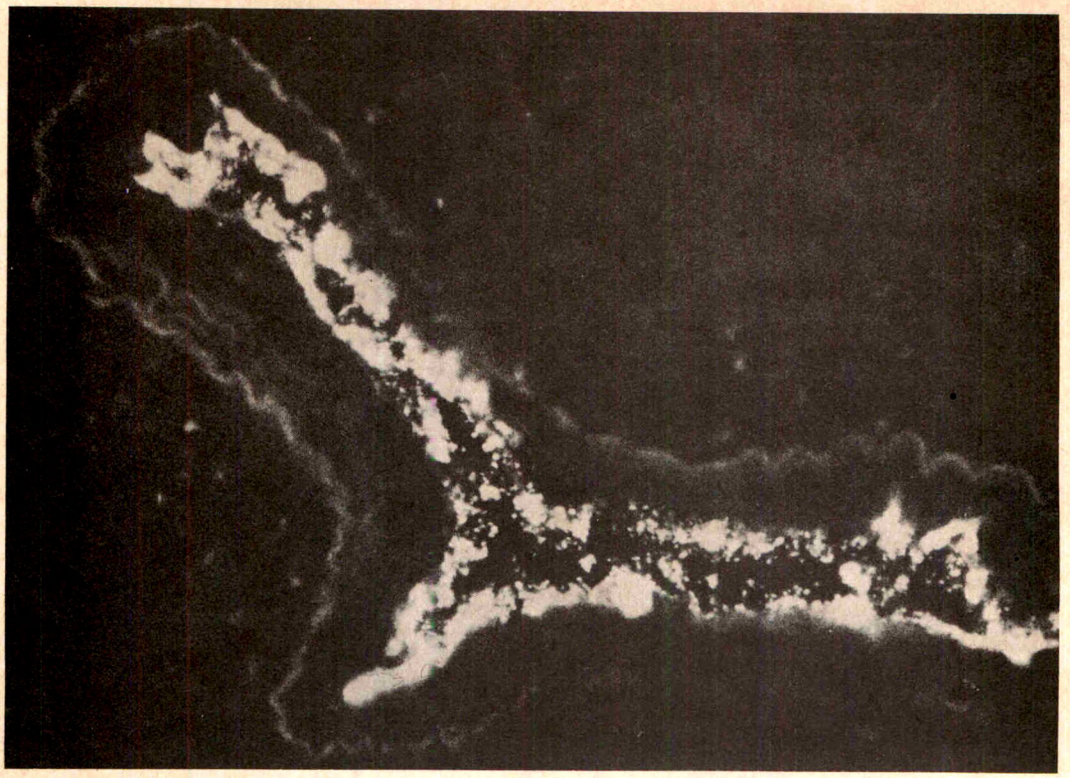


Fig. 1 (Pandolfi, Holmberg, and Turesson). Cross section of the central retinal artery a few millimeters from the eyeball showing FITC fluorescence of the intima. Note the autofluorescence of the elastic membrane (×250).

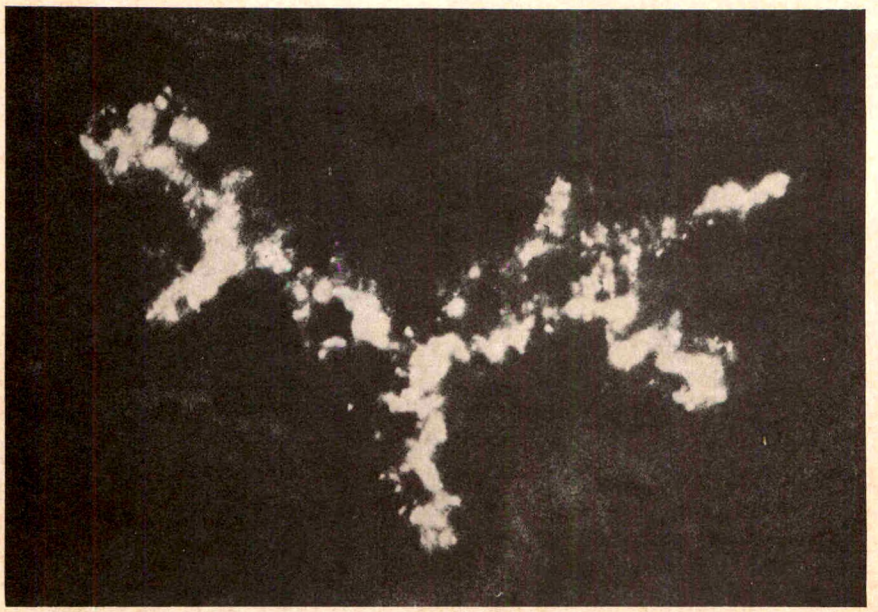


Fig. 2 (Pandolfi, Holmberg, and Turesson). FITC fluorescence of the intima of the central retinal vein (×250).

the pigment epithelium showed a strong autofluorescence (Fig. 3). The fetal retinal vessels were active also (Fig. 4). In the fetal eyes examined, we saw no activity at the site of the developing choroid and the pigment epithelium failed to show autofluorescence.

The fluorescence was totally blocked when the section was preincubated (after fixation) with a nonfluorescent antifactor VIII from another rabbit. The fluorescence was also completely blocked by adding excess antigen (prepared by gel chromatography of the cryoprecipitate in the presence of 3% dextran 40).[8] Dodecy sodium sulfate gel electrophoresis[9] of the antigen produced only one band, with approximately 180,000 to 190,000 mol. wt., that is, the fraction was homogeneous. These control experiments showed that the fluorescence was specific.



Fig. 3 (Pandolfi, Holmberg, and Turesson). FITC fluorescence of the intima of the intraocular branches of the central retinal artery and vein. Autofluorescence of the pigment epithelium (×250).

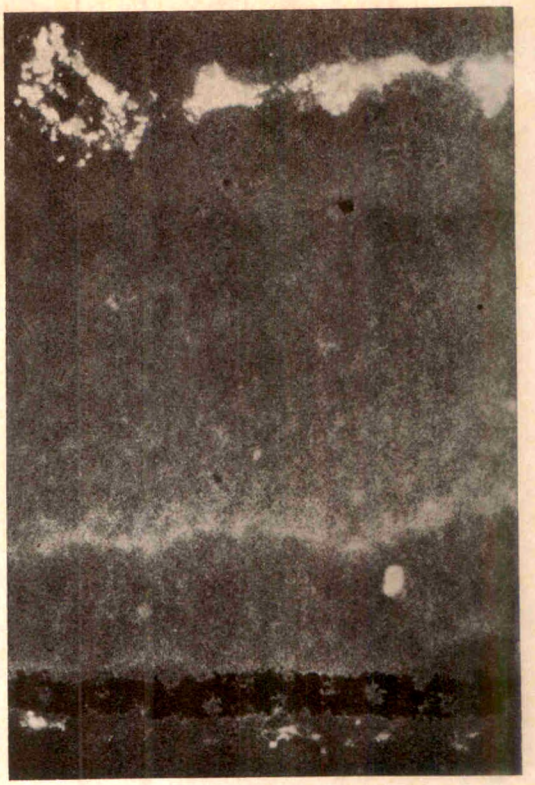


Fig. 4 (Pandolfi, Holmberg, and Turesson). FITC fluorescence of retinal vessels of the human fetal eye (crown to heel length: 22 cm). The pigment epithelium does not show any fluorescence (×250).

Examination of the same specimens by the fibrin slide technique regularly showed fibrinolytic activity confined to the site of the retinal vessels.

Discussion

The intima of several vessels contains an AHF-vWF immunologically related protein.[10,11] Our results showed this factor also is present in the intima of the retinal vessels

and coexists with an activator of fibrinolysis. Thus, the wall of the retinal vessels contains both factors promoting blood coagulation and platelet adhesion and factors promoting the opposite process, fibrin dissolution. Since these agents are localized to the intima they can directly react on release with the blood components and favor thrombus formation or thrombolysis. The occurrence of local fibrin deposition causing vascular occlusion followed by thrombolysis and rapid restoration of the lumen can explain the sudden onset of the occlusion of the retinal vessels and the failure to demonstrate thrombosis at autopsy[12] and blockade by fluorescein angiography.[13]

The finding in the retinal endothelium of a factor inducing the adhesion-aggregation of platelets is also compatible with the view that the first step in the development of diabetic retinopathy is occlusion of small arteries by aggregates of platelets followed by vascular congestion of the adjoining areas of the retina.[14] Patients with diabetes mellitus have an abnormally increased level of AHF-vWF in the blood and a decreased fibrinolytic activity.[15,16] These changes are profound, particularly in patients with retinopathy, and may reflect a similar alteration in the balance coagulation-fibrinolysis existing in the retinal vascular intima favoring the occlusion of the vessels.

Summary

By means of an immunofluorescent technique, we found factors promoting blood coagulation and platelet adhesion in the intima of retinal vessels. These factors coexisted with other agents causing the opposite process, fibrin dissolution. The components of this vascular hemostatic balance are possibly involved in the thrombotic occlusion of the retinal vessels, their canalization, and in the pathogenesis of diabetic retinopathy.

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PHOTOGRAMMETRIC ANALYSIS OF VOLUME ASYMMETRY OF THE OPTIC NERVE HEAD CUP IN NORMAL, HYPERTENSIVE, AND GLAUCOMATOUS EYES

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Photogrammetric analysis of the optic nerve head has become increasingly capable of providing highly quantified data concerning the geometry of the optic cup.[1-5] Technically it is a difficult process requiring the solution to a number of problems. The areas of greatest concern in this regard have been the disadvantages of film shrinkage, the errors of sequential stereophotography, and the reliability of the equations for converting photogrammetric measurements into millimeters on the disk.

The question of dimensional stability of the photographic medium has been solved by using only Kodak Estar base films which undergo essentially no shrinkage when air dried after development. By utilizing this material, the photographic image can be relied on to be of a constant size rather than the variable results previously obtained from acetate base films.[6]

Sequential stereophotography has been repeatedly shown to induce an error of from 10 to 25% because of the patient's eye movements between photographic frames.[3,4] Although I have tried a number of alternatives to this technique, such as the front-mounted biprism[3] and the stereoscopic slit-lamp camera,[5] the most effective solution seems to be the use of the Donaldson stereoscopic fundus camera, presently in production, which takes a simultaneous photograph.

Deriving a proper conversion equation for measurements has been aided by the work of Zeiss-Oberkochen whose camera has been used for stereophotography of the optic nerve head by most investigators. Although there has been some uncertainty concerning the actual focal length of this camera, a value of 41.5 mm was recently verified (according to personal communications from P. Hoerenz, Feb. 1 and Aug. 8, 1974), thus allowing the calculation of cup depth to be determined by $\triangle Z = 5.34 \times$ horizontal parallax. Obtaining the individual axial length of each eye by means of quantitative ultrasonography would be of additional value in achieving the utmost accuracy of this equation.

Having overcome these technical problems, perhaps the greatest remaining difficulty in using photogrammetric analysis as a diagnostic tool is the significant overlap of the range of geometric quantifiers for normal and glaucomatous optic cups[2] (Tables 1-3).[7] However, orifice area may be of at least some value in this regard. In the population sample studied, 25% of normal and ocular hypertensive patients had optic cup orifice areas of 1 mm^2 or less, whereas no glaucomatous eyes fell within this range. Subjects with orifice areas of greater than 1 mm^2 but less than 2 mm^2 had an 80% chance of being nonglaucomatous. In contrast, neither optic cup volume nor depth seem to offer any such diagnostic capability. For example, the volume of a congenitally large optic cup may well be greater than that of a congenitally small optic cup that has undergone only the earliest of glaucomatous atrophy. As a result, it is generally not possible to differentiate the majority of normal and glaucomatous optic nerve heads on the basis of their numeric measurements alone. The greatest value of photogrammetric analysis seems to lie in fol-

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Presented at the 1974 Glaucoma Symposium of the National Society for the Prevention of Blindness, Dallas, Texas, Oct. 6, 1974.

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TABLE 1

OPTIC CUP VOLUME

Classification (No. of Subjects)	0.01–0.08 (mm^3)	0.09–1.00 (mm^3)	1.01–1.80 (mm^3)
Normals (60)	13%	79%	8%
Ocular hypertensives (70)	26%	74%	0%
Glaucomas (50)	0%	80%	20%

lowing the same patients over a period of time and watching for measurable changes that may be harbingers of visual field loss.

To determine what additional data might be available in a "one-time" measurement, and with the knowledge that qualitative disk asymmetry is a fairly reliable sign of the presence of glaucoma in the larger cupped eye, I studied a series of patients' nerve heads with regard to the quantity of their asymmetry.

METHODS

Both eyes of 90 patients were refracted and underwent complete examinations including kinetic Goldmann and static Tübinger perimetry. Sequential stereophotographs of their optic nerve heads were taken by using Kodak Photomicrography color film 2483 (Estar base) in the Zeiss fundus camera with Allen stereoscopic separator set at 2.25 mm base. Each stereoscopic pair was inspected for accurate centering and then sent to a photogrammetric engineer who created a set of computer cards with optic disk contours coded in a digitized format. Four hundred to 700 data points per nerve head were selected for determination of the location of their x, y, and z coordinates. This information was projected on a 64×64-matrix where smooth curves were created by a computerized interpolation algorithm. The data were then handled by additional computer programs to determine the volume, depth, and orifice area for each optic cup.

TABLE 2

OPTIC CUP DEPTH

Classification (No. of Subjects)	0.01–0.24 (mm)	0.25–1.15 (mm)
Normals (60)	8%	92%
Ocular hypertensives (70)	9%	91%
Glaucomas (50)	0	100%

The only mathematic "decision" to be made independently for each nerve head was the location of the "top" of the cup. As previously described,[5] even disks without ophthalmoscopically obvious cups are extremely irregular in surface contour. The points on the rim of the optic cup are at a variable distance from the bottom of the cup, much as a ridge of mountain tops unevenly surrounds a valley. Various mathematic approaches to this problem have been attempted but the final standard solution has been to establish a plane through three reference points located at blood vessel crossings in the retina and move it gradually down the z axis of the nerve head until it first intersects with the entire rim of the cup. At this location the cup top is chosen.

Of the 90 patients chosen for this study 30 were bilateral normals (N/N): they were all under age 40, had intraocular pressures of 19 mm Hg or less, coefficients of outflow of 0.30 mm^3/min/mm Hg or more and full visual fields to all tests. The remaining 60 patients had two eyes in which the intraocular pressure was 20 mm Hg or more and a coefficient of outflow less than 0.18 mm^3/min/mm Hg. Of these patients, 35 had bilaterally normal appearing optic nerve heads and visual fields (OH/OH). Fifteen patients had one eye with a normal appearing optic disk and field while the fellow eye was in an early stage of glaucoma (OH/EG). In these subjects, the abnormal nerve head could be verified as being different from the normal one only by careful slit-lamp com-

TABLE 3

OPTIC CUP ORIFICE AREA

Classification (No. of Subjects)	0.04–1.0 (mm²)	1.04–1.96 (mm²)	2.00–4.24 (mm²)	4.28–6.20 (mm²)
Normals (60)	25%	35%	40%	0%
Ocular hypertensives (70)	24%	47%	28%	1%
Glaucomas (50)	0	20%	72%	8%

parison. Two different types of early glaucomatous disk changes could be distinguished. In the first, the prelaminar nerve tissue at the base of the cup displayed a moth-eaten appearance with loss of support of small blood vessels and an apparent deepening of the cup in that central area. This corresponds to Kronfeld's[8] description of central deep atrophy said to occur as a result of glaucoma in disks with congenitally small cups which, prior to the onset of atrophy, did not extend to the lamina. The second type, whose normal fellow eye had a cup which congenitally did reach to the lamina, demonstrated a similar moth-eaten appearance of nerve tissue located at the inferior or superior margin of its cup, or both. This corresponds to Kronfeld's phases of broad sector atrophy and upward or downward extension, both of which lead to vertical ovality of the cup. In no case did the excavation extend to the disk border, but, in all cases, an early field defect such as paracentral scotomata or nasal steps were the only perimetric changes found on both kinetic and static testing. The final ten patients were bilaterally glaucomatous having the combination of one eye with early disk and field changes while the other eye was more advanced in its disease (EG/G).

RESULTS

After quantitative geometric data had been calculated by the computer, the mathematic difference in optic cup volume, depth, and orifice area between the two eyes of a given patient was measured by subtracting the figures for the hypertensive eye from those for the glaucomatous eye. For the bilaterally normal, hypertensive, and glaucomatous subjects, subtraction of the smaller figure from the larger one was done routinely. Results were then tabulated according to the percentage of patients in each of the four subgroups which fell into a specific range of asymmetry (Tables 4-6).

Of the three geometric parameters measured, only volume asymmetry was sufficiently well distributed to be statistically significant ($P < .001$) and diagnostically useful, although both depth and orifice area may be of some assistance if a particular patient's optic cup measurements happen to fall into one of the population "tails." From these data it is evident that no person in this sample who was unilaterally glaucomatous had a cup volume asymmetry of less than 0.20 mm³. On the other hand, only 10% of the bilateral normals had a volume asymmetry of

TABLE 4

OPTIC CUP VOLUME ASYMMETRY

Classification (No. of Subjects)	0–0.19 (mm³)	0.20–0.30 (mm³)	0.31–1.31 (mm³)
N/N (30)	90%	10%	0
OH/OH (35)	80%	9%	11%
OH/EG (15)	0	53%	47%
EG/G (10)	0	40%	60%

TABLE 5

OPTIC CUP DEPTH ASYMMETRY

Classification (No. of Subjects)	0–0.3 (mm)	0.04–0.34 (mm)	0.35–0.46 (mm)
N/N (30)	17%	83%	0
OH/OH (35)	6%	91%	3%
OH/EG (15)	0	67%	33%
EG/G (10)	0	80%	20%

greater than 0.20 mm^3 and none of them exceeded 0.30 mm^3. In contrast, over half of the bilateral glaucoma patients studied had a cup volume asymmetry of greater than 0.30 mm^3.

DISCUSSION

Qualitative asymmetry of the optic nerve heads in a person's eyes is an early sign of glaucoma in the more cupped disk.[9-11] Asymmetry of the cup-disk ratio which has been determined by direct ophthalmoscopy occurs in less than 3% of normal people.[9] In addition, glaucoma is probably not a perfectly symmetrical process.[12] Examining patients stereoscopically with the slit lamp or by photograph makes it possible to see more qualitative characteristics of the optic nerve head than can be seen with the direct ophthalmoscope alone and increases the percentage of normal asymmetry which can be seen.[13] Thus, the more detailed the evaluation procedure, the greater the diagnostic information which can be obtained. In the area of visual fields this has occurred in the hands of thorough investigators by the advent of Goldmann and Tübinger perimetry.[14]

That quantification of the amount of asymmetry of a person's optic nerve heads can be of further help in the diagnosis of glaucoma does not appear to be a departure from this philosophy and was supported by Holm and associates.[2] It might be asked, however, whether this analytic method is more accurate than ocular fundus biomicroscopy in performing the same task. As previously noted, the unilateral glaucomatous patients in this investigation are representative of the early phases of nerve head atrophy which can be difficult to recognize with certainty. In these cases, even the cup-disk ratios were remarkably symmetrical as reflected in the data on optic cup orifice asymmetry (Table 6). Because the usefulness of more subtle clues to the earliest optic disk changes is yet to be widely and firmly established, the measurement of optic cup volume asymmetry appears to provide an important additional diagnostic dimension. Whether this procedure can differentiate a normal from a glaucomatous eye before quantitative perimetry of a particular patient does so, remains to be examined.

Through the ongoing process of longitudinal photogrammetric analysis of optic cups of patients who are theoretically at high risk of glaucomatous optic atrophy, the answer may eventually evolve. In the mean-

TABLE 6

OPTIC CUP ORIFICE AREA ASYMMETRY

Classification (No. of Subjects)	0–0.15 (mm^2)	0.16–1.6 (mm^2)	1.64–3.04 (mm^2)
N/N (30)	20%	80%	0
OH/OH (35)	11%	78%	11%
OH/EG (15)	7%	73%	20%
EG/G (10)	0	70%	30%

time, some attention can be given to the data on asymmetry which are already available for this population. Of the bilateral ocular hypertensive patients in this study, 80% had an amount of optic cup volume asymmetry that fell within the "definitely normal" range. The other 20% were more asymmetric and approximately half of them fell into a range beyond that of "normal." If in the ensuing years this latter group develops visual field changes, and the amount of optic cup asymmetry increases in hypertensive patients prior to the development of perimetric defects, then quantitative analysis of the symmetry of a patient's nerve heads may become a predictive tool for the onset of glaucoma. Clearly, only accurate perimetry studies and error free measurement of optic cups over a sufficiently long period of time will be able to answer this question with finality.

Summary

Recent studies of optic cup volume, depth, and orifice area demonstrated a large overlap of the range of these factors for normal and glaucomatous eyes, suggesting that it is usually not possible to distinguish abnormal disks on the basis of a particular set of geometric quantifiers.

Because of the knowledge that qualitative asymmetry of a person's optic cups may be a sign of glaucoma, calculation of the quantity of cup asymmetry using the aforementioned geometric parameters was undertaken in 90 patients. Results indicated that 90% of the bilaterally normal subjects who were studied and 80% of the ocular hypertensives had less than 0.20 mm^3 cup volume asymmetry. In contrast, however, all of the unilateral glaucoma patients in this sample exceeded that value. It therefore appears that measurement of the amount of, volume asymmetry between a person's optic cups may be a useful tool in the diagnosis of glaucoma.

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GONIOSCOPIC DIFFERENCES BETWEEN PRIMARY OPEN-ANGLE GLAUCOMA AND NORMAL SUBJECTS OVER 40 YEARS OF AGE

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Although gonioscopic abnormalities occur in patients with congenital and juvenile glaucoma, their presence in patients with open-angle glaucoma has been debated. A comparison between primary open-angle glaucoma and normal subjects should not be limited to a search for qualitative differences but should also include quantitative differences in the frequency distribution of various features.

A lower incidence of blood reflux into Schlemm's canal in primary open-angle glaucoma was noted by several authors.[1-10] Excluding pigmentary glaucoma, excessive trabecular pigmentation in primary open-angle glaucoma was observed by some investigators[11-14] but not by others.[6,15] An excess of felt-like or woolly substance in primary open-angle glaucoma was also observed.[6,16,17] The central anterior chamber depth is slightly shallower in primary open-angle glaucoma compared with carefully matched normal control subjects.[18-21] Lichter and Shaffer[22] found a higher incidence of iris processes inserting anterior to the scleral spur in primary open-angle glaucoma as compared with normal subjects. This is a further study of gonioscopic differences.

SUBJECTS AND METHODS

We selected normal and primary open-angle glaucoma subjects, over the age of 40, from the clinic, private practice, and volunteers. All subjects had a complete ocular examination, and Goldmann perimetry studies were performed on all glaucoma patients. Gonioscopy was performed in all four quadrants of one or both eyes with the Goldmann three-mirror goniolens and the Haag-Streit 900 slit lamp. Subjects with a contributory history of ocular trauma, ocular surgery, or significant anterior segment disease other than cataract, in both eyes, were excluded. In addition, a subject was disqualified if the angle was not medium to wide open in at least two quadrants, according to Shaffer's classification.[23] One observer performed all gonioscopic examinations.

We thought angle features would show a better correlation with ocular pressure rather than with disk or visual field changes and the subjects were classified primarily by pressure. The first group—normal subjects—had applanation pressures in both eyes equal to or less than 20 mm Hg on at least two occasions, and normal disks. They were subdivided into two subgroups: a larger group with no known family history of glaucoma and a smaller one with a history of glaucoma in a first-degree relative. The second group—primary open-angle glaucoma patients and suspects—had applanation pressures over 20 mm Hg in one or both eyes on at least two occasions. This group could have been subdivided either into those with definite visual field loss, or not, or those receiving medication, or not. We thought the latter might be a more pertinent factor in relation to angle features. Subjects receiving or those who had received medication had the more severe cases, with 60% of them having definite glaucomatous visual field loss. Subjects without a history of medication had a 4% incidence of definite visual field loss caused by glaucoma.

The glaucomatous group and the larger subgroup of normal subjects with a noncontributory history were individually matched

From the Combined Program in Ophthalmology, University of Alabama and the Eye Foundation Hospital, Birmingham, Alabama. This study was supported by grant-in-aid 5R01-EY01119, National Eye Institute.

Presented before the 102nd American Ophthalmological Society meeting, Hot Springs, Virginia, May 29, 1975.

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TABLE 1

SUBJECTS

Age Group, yrs in decades	Normal Subjects		Primary Open-Angle Glaucoma Patients				Normal Subjects With Family History of Glaucoma	
			Black		White			
	Black	White	No Medication History	Contributory History of Medication	No Medication History	Contributory History of Medication	Black	White
40–49	7	1	3	4	1	0	1	0
50–59	17	7	6	11	1	6	5	1
60–69	30	20	5	25	7	13	0	3
70–79	16	6	3	13	1	5	0	0
80–89	4	1	0	4	0	1	0	0
90–99	1	0	0	1	0	0	0	0
			17	58	10	25		
Total	75	35	75		35		6	4

by race (black or white) and age (in decades), by using random exclusion of subjects in a given category from the larger group until a match was obtained (Table 1). Only one eye of each subject was included in the analysis. The right eye was selected unless it was excluded by these criteria.

Although normal and glaucomatous subjects were not matched individually by refractive error, this measurement was available in 206 of the 230 subjects. In 101 normal subjects, with no known contributory glaucoma history, the distribution by spherical equivalent was as follows: 46% of subjects had more than +1.00 diopter hyperopia, 46% were between +1.00 and −1.00, and 9% had more than −1.00 myopia. The analogous distribution in 95 glaucoma subjects was 29, 46, and 24% respectively. There were more myopes in the glaucoma group. All normal subjects had between +5.00 and −5.00 diopters. In the glaucoma group three subjects had more than −5.00 myopia and two had more than +5.00 hyperopia.

The various angle features studied and the numeric method of grading each one were compiled (Table 2). The degree of abnormality increased with the grade number. The iris root normally inserts into the ciliary body with a grade of 0, while the other grades refer to a more anterior or higher insertion. The term iris process refers to what some observers call mesodermal remnants, rudimentary pectinate fibers, or uveal

TABLE 2

ANGLE FEATURES AND CLASSIFICATION

Feature	Grade			
	3	2	1	0
Pigmentation of trabeculae	Marked	Moderate	Minimum	None
Insertion of iris root	To Schwalbe's line	To trabeculae	To scleral spur	To ciliary body
Prominence of Schwalbe's line	Marked	Moderate	Minimum	None
No. of iris processes				
To ciliary body band	Marked	Moderate	Minimum	None
To trabeculae	Marked	Moderate	Minimum	None
To Schwalbe's line	Marked	Moderate	Minimum	None

meshwork. Each quadrant was graded separately. In a small percentage of eyes, one or more quadrants could not be graded for the insertion of iris root or iris processes to the ciliary band because an iris roll prevented an adequate view of the angle.

To simplify the presentation and analysis of data, we calculated a mean value and standard deviation from the frequency distribution of grades for each angle feature. Statistical analysis was based on the number of subjects rather than the number of quadrants. Statistical comparison of means was done with the Student's t-test. The F test was also used for analysis of variance among groups. A two-tailed test was used for determining probability values.

Results

In normal eyes the trabecular pigmentation was most marked inferiorly, followed by the nasal quadrant. The number of iris processes to the trabecular meshwork was most marked nasally, followed by the inferior quadrant.

Table 3 shows the degree of trabecular pigmentation by age for both normal and glaucomatous subjects. There was no statistically significant trend with age for either group. However, an inspection of the data between the fourth and eighth decades, the age range of most of the subjects, shows steady decreases in pigmentation in normal subjects but only minimal decreases in glaucomatous patients in the sixth decade.

Black and white subjects were generally similar in both groups. There were more iris processes to the trabeculae in blacks but this may have been caused by better visualization of the processes in the more pigmented eye. Trabecular pigmentation appeared to be greater in whites but this could have been caused by a better contrast in the less pigmented eye.

TABLE 3

TRABECULAR PIGMENTATION BY AGE, GRADING BY MEAN ±S.D.

Age Groups, yrs	No. of Subjects	Subjects	
		Normal	Glaucomatous
40–49	8	0.63±1.06	1.50±0.76
50–59	24	0.91±0.72	1.33±1.05
60–69	50	0.82±0.75	1.20±0.81
70–79	22	0.64±0.66	1.41±0.91
80–89	5	1.00±0.71	1.20±1.30

To compare the glaucoma and normal groups, the black and white subjects were combined. An analysis of blacks and whites separately gave similar results. Table 4 presents the values for the various angle features in the four groups. Based on these data, Table 5 presents the statistical comparisons among the groups. Glaucoma patients with medication had more trabecular pigmentation, higher insertion of the iris root, and more iris processes at all levels than the normal subjects. Glaucoma patients with medication also had greater trabecular pigmentation and more iris processes than glaucoma patients without medication. Normal subjects with a family history had a higher insertion of the iris root and a more prominent Schwalbe's line than normal subjects without a family history. The values were almost consistently higher in the former group (Table 4). The few subjects in this group probably mask a statistically significant difference for more individual features.

Table 6 shows the relationship between refractive error and two angle features in the normal and glaucomatous subjects. There was no statistical interaction in that both groups showed a similar relationship with refractive error. Myopes had significantly more trabecular pigmentation ($P < .05$) and iris processes ($P < .01$). In all categories, the findings were more marked in the glaucoma group ($P < .001$).

Discussion

Our findings that iris processes are most marked nasally agree with the observations of Chandler and Grant[24] and Lichter.[25] Our observation that trabecular pigmentation does not vary with age in normal subjects appears to differ with the widespread view that pig-

TABLE 4

ANGLE FEATURES IN FOUR GROUPS OF SUBJECTS,* GRADING BY MEAN ± S.D.

	Normal (110)	Normal with Family History (10)	Glaucoma without Medication (27)	Glaucoma with Medication (83)
Pigmentation of trabeculae	0.79 ± 0.74	1.20 ± 1.03	1.07 ± 0.87	1.39 ± 0.88
Insertion of iris root	0.01 ± 0.10	0.22 ± 0.45	0.24 ± 0.44	0.18 ± 0.39
Prominence of Schwalbe's line	0.05 ± 0.27	0.50 ± 0.71	0.19 ± 0.48	0.13 ± 0.41
No. of iris processes				
To ciliary body band	1.82 ± 0.81	2.29 ± 0.76	2.05 ± 0.97	2.42 ± 0.69
To trabeculae	0.73 ± 0.72	1.10 ± 0.88	1.07 ± 0.87	1.52 ± 0.86
To Schwalbe's line	0 ± 0	0 ± 0	0.04 ± 0.19	0.14 ± 0.50

* Parentheses indicate number of subjects in each group.

TABLE 5

STATISTICAL COMPARISON OF ANGLE FACTORS AMONG VARIOUS GROUPS OF SUBJECTS* ($P < .1$)

	Normal (110) to Glaucoma with Medication (83)	Glaucoma with Medication (83) to Glaucoma without Medication (27)	Normal (110) to Normal with Family History (10)
Pigmentation of trabeculae	$< .001$	$< .1$	—
Insertion of iris root	$< .001$	—	$< .05$
Prominence of Schwalbe's line	—	—	$< .001$
No. of iris processes			
To ciliary body band	$< .001$	$< .1$	—
To trabeculae	$< .001$	$< .01$	—
To Schwalbe's line	$< .01$	$P = .12$	—

* Parentheses indicate number of subjects in each group.

TABLE 6

ANGLE FEATURES BY REFRACTIVE ERROR, SPHERICAL EQUIVALENTS IN DIOPTERS, GRADING BY MEAN ± S.D.

	Hyperopia +1.00*	From +1.00 to −1.00*	Myopia −1.00†
Pigmentation of trabeculae			
Normal	0.76 ± 0.74	0.83 ± 0.77	1.22 ± 1.09
Glaucomatous	1.18 ± 0.82	1.19 ± 0.85	1.46 ± 1.06
No. of iris processes to trabeculae			
Normal	0.70 ± 0.66	0.70 ± 0.73	1.00 ± 0.71
Glaucomatous	1.30 ± 0.79	1.28 ± 0.88	1.88 ± 0.95

* In 46 normal and 28 glaucomatous subjects.
† In 9 normal and 24 glaucomatous subjects.

mentation increases with age. The explanation of this difference may be that in normal subjects, trabecular pigmentation increases from infancy to middle age but decreases after that. In primary open-angle glaucoma, there is a greater degree of trabecular pigmentation at all ages. If, in glaucoma patients between the ages of 50 and 80 years, there are two effects on trabecular pigmentation (a tendency to decrease with normal aging and a tendency to increase from the disease process), the unusual minimum in the 60s could be explained. Perkins[26] also noted a similar but less marked decrease in trabecular pigmentation in the 60s.

A comparison between primary open-angle glaucoma and normal subjects shows a shift in the frequency distribution of several angle features. The increased incidence of iris processes at all levels in glaucoma confirms and extends the findings of Lichter and Shaffer.[22] Others[11-14] noted increased trabecular pigmentation in glaucoma. The higher insertion of the iris root in glaucoma is a new finding. Although there is a higher percentage of myopes in our glaucoma group, and myopes show increased values for some angle features, this cannot explain the difference between the normal and glaucomatous groups. For each refractive level the values were higher for the glaucomatous group.

Nesterov and co-workers[27,28] noted a difference in the configuration of structures adjacent to the canal of Schlemm between normal and primary open-angle glaucoma subjects. In glaucoma the canal was displaced anteriorly in relation to the apex of the angle, the scleral spur was swollen, and the meridional fibers of the ciliary muscle were inserted more posteriorly. Rohen[29] had previously noted a smaller scleral spur. The finding of a more anterior position of Schlemm's canal in glaucoma seems to contradict our finding of a more anterior or higher insertion of the iris root. In addition, the possible effect of refractive error was not studied. Nevertheless, the existence of differences in the angle structure between normal and primary open-angle glaucomatous subjects is highly likely.

It is important to know which abnormal gonioscopic findings precede and which follow the onset of elevated pressure. The many iris processes and the high insertion of the iris root are almost certainly present at birth and thus precede the abnormal pressure. The temporal relationship to trabecular pigmentation is uncertain although our clinical impression is that the pigmentation both precedes and follows the elevation of pressure.

An association between findings is not equivalent to a causal relationship. Nevertheless, we agree with Lichter and Shaffer[22] that congenital angle anomalies play a role in the pathogenesis of the elevated pressure. That the more severe cases show more congenital angle anomalies fits this concept. The physiologic counterpart to these visible congenital angle anomalies is uncertain. Nesterov and co-workers[27,28] presented evidence to show that the configuration of the angle in primary open-angle glaucoma facilitates the compression of Schlemm's canal by movement of the trabecular meshwork toward the outer wall of the canal. We also suggest that the physiologic counterpart of the congenital anomalies observed by gonioscopy is a pressure sensitivity of the outflow facility[30,31] that is greater in glaucoma.[31]

Apparently congenital angle anomalies cannot be the sole factor in the pathogenesis of the elevated pressure. These anomalies are present in some eyes with normal pressure and absent in other eyes with elevated pressure. In addition, the incidence of primary open-angle glaucoma increases with age. One can only speculate on the nature of the other factor or factors. Perhaps an added aging effect on the trabecular meshwork produces a progressive decrease in the facility of outflow. We speculated[32,33] that aqueous hypersection is the second key factor.

Summary

Gonioscopy was performed on 110 patients with primary open-angle glaucoma over 40

years of age and an equal number of normal subjects, matched by race and age. The frequency distribution of various angle features differed in the two groups: in the glaucoma group, there were more iris processes at all levels of insertion, a higher insertion of the iris root, and more trabecular pigmentation. A congenital angle anomaly is one important factor in the pathogenesis of the elevated pressure.

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BLINDNESS FROM GLAUCOMA

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Present day medicine and surgery are believed capable of preventing blindness from glaucoma, provided it is recognized and treated early.[1] It is therefore distressing to find that glaucoma continues to be one of the leading causes of blindness in the United States today, especially among nonwhites.[2]

In this study we had the following objectives: (1) to present, in some detail, recent data derived from the U.S. Model Reporting Area for Blindness Statistics (MRA); (2) to assess trends in blindness due to glaucoma by comparing recent MRA data with earlier years; and (3) to compare MRA findings with other available data on blindness from glaucoma with respect to risk factors and trends.

Description of the MRA—Our source of the new data is the MRA for Blindness Statistics for which detailed descriptions are available elsewhere.[3,4] For convenience, the MRA consists of a group of state blindness registries that maintain statistics according to a common definition of blindness—visual acuity of 20/200 or less in the better eye with best correction or visual field limited to 20 degrees in its widest diameter[5]—and follow common rules for coding and updating records. The MRA began in 1962 with nine states and the number gradually increased to 16 states by 1970, the most recent year for which MRA data are available.

It is generally assumed that the MRA data understate new cases of blindness. The degree of understatement is not known, but rough indications[6-8] suggest that the true incidence of blindness may be as much as twice the register incidence. However, we emphasize internal comparisons among various subgroups rather than the absolute level of registration.

Recent register incidence and prevalence rates per 100,000 population by sex and race are limited to 14 states because detailed data in the required format were not available from Massachusetts or New York (Tables 1-5).

Both crude and age-standardized rates are shown. The crude rates are simply the total number of cases ($\times$100,000) divided by the corresponding total population. Age-standardized rates* were computed according to the direct method[9] with the age distribution of the total 1970 census population of the 14 states as standard, and are used to adjust for different proportions of younger and older persons among the various groups. Population data for 1969 and 1970 are the July 1 estimates for the resident state population[10] with the age-color-sex details apportioned as in the 1970 census for the corresponding state. MRA data for 1963 to 1968 were taken or derived from the published MRA monographs for those years.[11-16]

Unless otherwise specified, the specific cause data in all tables in this paper are restricted to single causes of blindness and are derived from the diagnostic reports on persons registered as blind with the appropriate state agency. Glaucoma in the MRA includes primary glaucoma, both chronic simple and narrow angle, and glaucoma not specified as either primary or secondary. We excluded glaucoma specifically reported as

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* The age-standardized rate is computed as

$$P'u = \frac{\Sigma N_{is} P_{iu}}{\Sigma N_{is}}$$

where

P_{iu} = rate/100,000 in age group i of population u
N_{is} = number in age group i of standard population
Σ is a symbol for addition, in this case addition over all age groups.

secondary or congenital from the glaucoma category in this paper. Of the known primary cases in the 1969-1970 MRA, chronic simple glaucoma accounts for 89%.

RESULTS

MRA by cause, sex, race, and age—1969 to 1970—Additions to blindness registers from 1969 to 1970 and persons on the registers as of Dec. 31, 1970, for 14 MRA states were compiled by cause and sex (Table 1) and by cause and race (Table 2). Glaucoma was a leading cause of blindness in the U.S. (Tables 1 and 2). The age-standardized rates showed that glaucoma ranks as the third leading cause of blindness.

The rates of blindness from glaucoma were slightly higher for men than for women, true for both register incidence and register prevalence (Table 1). While blindness from glaucoma still ranked high among whites, it was the major cause of blindness for nonwhites (Table 2). (The composition of known nonwhites in the 1970 14-state MRA population was 97.5% black, 1.7% native American, and 0.8% other.) The ratio of nonwhites to whites in the age-standardized rates of glaucoma for additions to register and total on register was 8.3 and 8.4 respectively, as compared to 2.0 and 2.2 for all other causes. If we calculated age-standardized rates for glaucoma with or without other associated causes of blindness and included a proportional allocation of unknown causes, then the ratio of

TABLE 1

AVERAGE ANNUAL ADDITIONS TO BLINDNESS REGISTERS 1969–1970 AND PERSONS ON THE REGISTERS DEC. 31, 1970, BY CAUSE AND SEX (14 MRA STATES)

Cause	Average Annual Additions, 1969–1970				Persons on Register Dec. 31, 1970			
	Total	Men	Women	Men/Women Ratio	Total	Men	Women	Men/Women Ratio
	Number							
Glaucoma	544	276	268	—	6,059	2,909	3,150	—
Cataract	778	321	457	—	7,202	3,235	3,967	—
Diabetic retinopathy	464	172	292	—	2,575	947	1,628	—
Retinal (other than diabetic retinopathy)	1,121	508	613	—	11,142	5,428	5,714	—
Optic nerve	352	213	139	—	5,042	2,997	2,045	—
Uveitis	154	72	82	—	2,822	1,394	1,428	—
Cornea or sclera	136	65	71	—	2,584	1,204	1,380	—
Myopia	118	62	56	—	1,627	849	778	—
All causes* except glaucoma	4,784	2,161	2,623	—	48,824	23,991	24,833	—
	Age-Standardized Rate/100,000							
Glaucoma	1.46	1.68	1.27	1.3	16.2	18.2	14.6	1.2
Cataract	2.07	1.89	2.17	0.9	19.2	19.5	18.7	1.0
Diabetic retinopathy	1.23	0.94	1.46	0.6	6.9	5.5	7.9	0.7
Retinal (other than diabetic retinopathy)	2.98	3.06	2.90	1.1	29.7	32.5	27.0	1.2
Optic nerve	0.96	1.17	0.69	1.7	13.5	17.2	10.3	1.7
Uveitis	0.40	0.42	0.42	1.0	7.5	8.1	7.1	1.1
Cornea or sclera	0.36	0.37	0.35	1.1	6.9	7.1	6.7	1.1
Myopia	0.31	0.34	0.28	1.2	4.3	4.8	3.9	1.2
All causes* except glaucoma	12.78	12.68	12.70	1.0	130.3	140.7	120.2	1.2

* Includes retrolental fibroplasia, multiple affections, other and unknown causes.

TABLE 2

AVERAGE ANNUAL ADDITIONS TO BLINDNESS REGISTERS 1969-1970 AND PERSONS ON THE REGISTERS DEC. 31, 1970, BY CAUSE AND RACE (14 MRA STATES)

Cause	Average Annual Additions, 1969–1970				Persons on Register Dec. 31, 1970			
	Total	White	Non-white	Nonwhite/White Ratio	Total	White	Non-white	Nonwhite/White Ratio
	Number							
Glaucoma	544	250	294	—	6,059	2,832	3,227	—
Cataract	778	582	196	—	7,202	5,253	1,949	—
Diabetic retinopathy	464	349	115	—	2,575	1,951	624	—
Retinal (other than diabetic retinopathy)	1,121	983	138	—	11,142	9,466	1,676	—
Optic nerve	352	248	104	—	5,042	3,257	1,785	—
Uveitis	154	105	49	—	2,822	1,853	969	—
Cornea or sclera	136	79	57	—	2,584	1,578	1,006	—
Myopia	118	82	36	—	1,627	1,216	411	—
All causes* except glaucoma	4,784	3,692	1,092	—	48,824	36,712	12,112	—
	Age-Standardized Rate/100,000							
Glaucoma	1.46	0.78	6.51	8.3	16.2	8.6	72.0	8.4
Cataract	2.07	1.80	4.13	2.3	19.2	16.1	40.7	2.5
Diabetic retinopathy	1.23	1.05	2.50	2.4	6.9	5.9	13.6	2.3
Retinal (other than diabetic retinopathy)	2.98	2.99	2.82	0.9	29.7	28.9	35.0	1.2
Optic nerve	0.96	0.79	2.03	2.6	13.5	10.1	37.5	3.7
Uveitis	0.40	0.32	0.99	3.1	7.5	5.7	20.4	3.6
Cornea or sclera	0.36	0.24	1.16	4.8	6.9	4.8	21.3	4.4
Myopia	0.31	0.27	0.62	2.3	4.3	3.8	7.9	2.1
All causes* except glaucoma	12.78	11.39	22.24	2.0	130.3	112.9	250.3	2.2

* Includes retrolental fibroplasia, multiple affections, other and unknown causes.

nonwhite to white was 7.4 for additions to register and 7.1 for total on 1970 register.

To learn if this seven- to eightfold ratio for nonwhites compared to whites applied to individual states, we computed age-standardized rates by race for each of the 14 MRA states. When the number of nonwhites on the register for glaucoma blindness was over 15 persons, no state had a ratio of less than 7:1 (Table 3).

We observed the large differential between nonwhite and white rates for both men and women (Table 4). Men and women of both races experienced rapid increase in frequency of blindness with age. Age-specific rates of blindness from glaucoma in nonwhites were higher than in whites for every age group, with the greatest difference noted at 45 to 64 years, where the ratio of nonwhite to white rates was almost 15:1. The ratio of nonwhite 1970 addition rates to those for whites showed the nonwhite at higher risk for blindness at every blindness level from 20/200 to absolute blindness (Table 5).

Trend in MRA data—1963 to 1970—We compiled the available data on trend of glaucoma blindness during 1963 to 1970 (Table 6). The rates came from the cases added to registers and the state populations in the Statistics on Blindness Series.[2,11–16] To minimize bias, the blindness rates from glaucoma were calculated each year, beginning with 1963, on a constant group of states. The rate of register incidence for blindness from glau-

TABLE 3

NUMBER AND AGE-STANDARDIZED RATE/100,000 OF PERSONS ON REGISTERS DEC. 31, 1970, BECAUSE OF GLAUCOMA BY STATE AND RACE
(14 MRA STATES)

State	White		Nonwhite		Nonwhite/White Ratio of Rates
	No.	Rate/100,000	No.	Rate/100,000	
All states	2,832	8.6	3,227	72.0	8.4
Connecticut	202	6.4	66	60.4	9.4
Georgia	171	5.4	583	59.6	11.0
Kansas	198	7.0	62	58.6	8.4
Louisiana	295	12.4	870	92.6	7.5
New Hampshire	96	11.2	0	*	—
New Jersey	655	9.3	347	68.2	7.3
New Mexico	63	8.3	6	*	—
North Carolina	462	12.6	906	99.7	7.9
Oregon	265	10.8	12	*	—
Rhode Island	81	7.4	7	*	—
South Dakota	46	5.5	5	*	—
Utah	42	4.8	2	*	—
Vermont	32	6.2	0	*	—
Virginia	217	6.4	359	48.0	7.5

* Rates not computed on less than 15 cases. Totals do not add because of rounding in allocation of unknown race.

TABLE 4

PERSONS ON BLINDNESS REGISTERS DEC. 31, 1970, DUE TO GLAUCOMA BY SEX, RACE, AND AGE
(14 MRA STATES)

	Total*	Age, yrs						
		<5	5–19	20–44	45–64	65–74	75–84	85+
		Rates per 100,000 Population						
White								
Men	9.5	†	†	1.2	9.3	42.9	104.5	285.7
Women	7.9	†	†	0.6	8.3	30.9	92.5	248.6
Total	8.6	†	0.1	0.9	8.8	36.1	97.2	261.4
Nonwhite								
Men	81.1	†	†	9.5	154.9	430.2	637.2	707.7
Women	64.5	†	†	5.9	111.1	356.0	534.4	773.7
Total	72.0	†	†	7.6	131.4	388.3	576.9	746.9
		Ratios of Rates						
Nonwhite/White								
Men	8.5	—	—	7.9	16.7	10.0	6.1	2.5
Women	8.2	—	—	9.8	13.4	11.5	5.8	3.1
Total	8.4	—	—	8.4	14.9	10.8	5.9	2.9
Men/Women								
White	1.2	—	—	2.0	1.1	1.4	1.1	1.1
Nonwhite	1.3	—	—	1.6	1.4	1.2	1.2	0.9
Total	1.2	—	—	1.6	1.2	1.3	1.2	1.1

* Age-standardized rates.
† Rates not computed on less than 15 cases.

TABLE 5

ADDITIONS TO REGISTERS IN 1970 DUE TO GLAUCOMA AND TO ALL CAUSES EXCLUDING GLAUCOMA BY RACE* AND BLINDNESS CATEGORY (14 MRA STATES)

Blindness Category	Glaucoma			Causes Other Than Glaucoma		
	White	Nonwhite	Nonwhite/ White Ratio	White	Nonwhite	Nonwhite/ White Ratio
No.						
All blindness	218	271	—	3,244	985	—
Absolute blindness	15	27	—	187	69	—
LP to less than 5/200	51	64	—	756	298	—
5/200 to less than 20/200	46	37	—	919	225	—
20/200	34	42	—	1,024	287	—
Restricted field	69	96	—	166	43	—
Unknown	3	5	—	192	63	—
Rate/100,000						
All blindness	0.69	4.69	6.8	10.2	17.1	1.7
Absolute blindness	0.05	0.47	9.4	0.6	1.2	2.0
LP to less than 5/200	0.16	1.11	6.9	2.4	5.2	2.2
5/200 to less than 20/200	0.15	0.64	4.3	2.9	3.9	1.3
20/200	0.11	0.73	6.6	3.2	5.0	1.6
Restricted field	0.22	1.66	7.5	0.5	0.7	1.4
Unknown	†	†	†	0.6	1.1	1.8

* Unknown race excluded.
† Rates not computed on less than 15 cases.

coma was approximately constant from 1965 to 1970 (Table 6). The rate was higher in 1963 and 1964. However, since 1965 was the first year for which there was a high degree of centralized control of blindness cause coding, the MRA rates for 1963 and 1964 for specific causes of blindness are suspect.

DISCUSSION

Our main finding based on MRA data is the 7 to 8:1 ratio of blindness from glaucoma—7:1 with glaucoma in combination with other causes and 8:1 with glaucoma as the sole cause of blindness—in nonwhites as compared to whites as shown by the age-standardized rates. For those aged 45 to 64 years, the ratio is 15:1. We found that risk of blindness from glaucoma was slightly higher for men than for women; increased rapidly with age; and the rate of additions to blindness registers because of glaucoma remained fairly stationary from 1965 to 1970.

We should consider whether these findings, based on registered blindness, are representative of the true occurrence of blindness from primary glaucoma in the total population of MRA states. We already stated that MRA data are not absolutely correct because of substantial incompleteness of registration[6-8]; but are MRA data relatively useful?

We have no reason to suspect that the proportion of the population becoming blind due to glaucoma who are registered with state agencies increased or decreased appreciably from 1965 to 1970. Thus, without knowing whether the absolute values of the addition rates for glaucoma are correct, we can probably accept the finding of level trend as a reflection of the true situation over the past five years or so. The observed increase in risk with age is frequently reported. The excess risk for men over women is not great and there are many possibilities for differential completeness of registration between men and women.

The observed 8:1 ratio of blindness rates for nonwhites compared to whites probably results from one or more of the following four components:

1. A differential in reporting. Perhaps there really are not any more blind nonwhites from glaucoma than whites, but nonwhites may be more likely to be registered and reported, and therefore the observed rates are higher.

2. A greater amount of basic disease (for example, ocular hypertension, nonblinding glaucomatous field defects, and the like) in nonwhites as compared to whites.

3. A disproportionate failure of nonwhites to obtain treatment at an early point in the history of the disease to prevent blindness. It is possible that nonwhites and whites have equal amounts of glaucoma morbidity and are reported equally, but the rates are higher for nonwhite blindness from this disease compared to whites because nonwhites do not get medical attention early enough to prevent blindness.

4. Medical or surgical treatment of the underlying disease may be less effective in nonwhites than in whites.

Probably all four elements contribute to the observed ratio of about 8:1, and it is difficult, if not impossbile, for us to allocate their appropriate share.

Regarding the reporting differential, we do not know what the true rates would be if differentials in reporting completeness could be removed. Because of their lower economic status and greater contact with public agencies, nonwhite blindness registration is more complete than white registration. However, if the 7 or 8:1 ratio were simply an artifact resulting from more complete registration of blind nonwhites as compared to blind whites, the differential would be observed for other causes of blindness as well. No other cause of blindness shows a relative differential of this magnitude suggesting that reporting completeness cannot provide the entire explanation. Because the nonwhite to white ratio for absolute blindness is more than 9:1, we ruled out the possibility that nonwhite rates for glaucoma are relatively high only because more mild cases are included.

TABLE 6

ADDITIONS TO BLINDNESS REGISTERS BECAUSE OF GLAUCOMA* WITH FIXED GROUPS OF MRA STATES†

Year	No. of MRA States‡					
	10	11	13	14	15	16
1963	2.0	—	—	—	—	—
1964	2.2	2.0	—	—	—	—
1965	1.6	1.6	1.6	—	—	—
1966	1.6	1.5	1.5	1.5	—	—
1967	1.5	1.5	1.4	1.4	1.4	—
1968	1.7	1.6	1.6	1.6	1.6	—
1969	1.6	1.6	1.5	1.5	1.5	1.5
1970	1.5	1.5	1.4	1.4	1.4	1.5

* Limited to those examined by an ophthalmologist or eye, ear, nose, and throat specialist.

† Rates/100,000 population; source, MRA statistics for 1963 to 1970.

‡ Ten states: Connecticut, Kansas, Louisiana, Massachusetts, New Hampshire, New Jersey, North Carolina, Oregon, Rhode Island, and Vermont. 11 states: all plus Virginia; 13 states: all plus New Mexico and Utah; 14 states: all plus South Dakota; 15 states: all plus Georgia; 16 states: all plus New York.

Regarding the excess of underlying disease, in glaucoma survey data included as part of a food handler's examination (the bias of selection for the screening examination is probably at a minimum), the observed ratio of the prevalence of previously unrecognized glaucoma among nonwhites compared to whites was approximately 2:1.[17] These are limited data and it is improper to rely heavily on them, but they hint that the underlying disease component exists and that its size is perhaps 2:1.

Similarly, regarding reporting for treatment and success in results of treatment, there is evidence that nonwhites tend to present later in the stage of the disease than whites.[18] This effect, if true, does not extend so far as to include much delay after blindness is present. In these data we observed an average age of 70 years for whites and 62 years for nonwhites at registration.

Treatment results, particularly surgical outcomes, may be unsatisfactory in nonwhites.[19-22]

The MRA observation of a stationary trend of new blindness from glaucoma agrees with two other studies.[23,24] The rate of new blindness from glaucoma reported by the National Society for the Prevention of Blindness was 2.4/100,000 for 1957, 1960, and 1962.[23] A more recent study on incidence and causes of blindness in England and Wales from 1963 to 1968 referred to blindness from glaucoma for persons under 65 years of age. The calculated rate* of new glaucoma blindness for each year with 0.4/100,000. For comparison, the average 1969-1970 MRA glaucoma incidence rate is 0.3/100,000 for whites under age 65.[2]

Summary

We observed an overall ratio of 8:1 for nonwhite to white primary glaucoma blindness. Our fragmentary evidence suggested that the ratio of underlying disease, that is, nonblinding glaucoma or intraocular pressure differentials, may be closer to 2:1 than 8:1 as between nonwhites and whites. The remaining fourfold differential can be explained by a combination of the following: more complete reporting for nonwhites, reporting for medical care later in the disease than whites, and poorer response to treatment for nonwhites compared to whites.

The trend of new blindness from glaucoma for recent years was stationary in the United States, England, and Wales.

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OPHTHALMIC MINIATURE

"Keep your eyes open!" called out the sailors.

And they were opened widely. Both eyes and glasses, a little dazzled, it is true, by the prospect of two thousand dollars, had not an instant's repose. Day and night they watched the surface of the ocean, and even nyctalopes, whose faculty of seeing in the darkness multiplies their chances a hundredfold, would have had enough to do to gain the prize.

Jules Verne, *20,000 Leagues Under the Sea*
New York, Scribner, 1925

ACUTE GLAUCOMA IN SYSTEMIC MUCOPOLYSACCHARIDOSIS I-S

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We observed acute glaucoma requiring surgical intervention in each eye of a brother and sister with systemic mucopolysaccharidosis (MPS) type I-S (Scheie's syndrome).[1,2] While angle closure seemed the most likely mechanism for sudden increased pressure, the cloudy corneas characteristic of this syndrome made gonioscopic evaluation impossible. Glaucoma has not been documented in the systemic MPS diseases, though megalocornea (without increased intraocular pressure) was reported in MPS I-H (Hurler's),[3,4] and MPS IV (Morquio's).[5]

We present two cases of possible abnormal acid mucopolysaccharide (AMP) deposition in acute glaucoma.

CASE REPORTS

Case 1—This 56-year-old white man, first examined in 1962, had a history of joint stiffness, decreased night vision, and manifest cloudy corneas. Visual acuity was 20/40, with each eye corrected by +3.50 +1.50 ×180. The corneas had dense ground-glass opacity, greatest peripherally. There were retinitis pigmentosa-like retinal changes, with normal optic disk and cup. Intraocular pressure in both eyes was 12 mm Hg (Schiøtz). Perimetry studies showed a 30-degree-wide ring scotoma sparing the central 5 degrees in each eye, and the electroretinogram (ERG) showed decreased scotopic and nearly normal photopic components. The x-ray films and mucopolysaccharidiuria (predominantly dermatan sulfate), combined with no α-L-iduronidase enzyme activity in cultural skin fibroblasts, confirmed the diagnosis of Scheie's syndrome.

The intraocular pressure and disk remained normal for seven years, but corneal opacity progressed and the cornea appeared two to three times the normal thickness in its periphery.

On Jan. 30, 1969, the patient presented with severe pain in the right eye of three days' duration; bullous keratopathy; anterior uveitis with keratic precipitates; intraocular pressure, 75 mm Hg (applanation); and visual acuity was light perception. Gonioscopic examination was prevented by corneal opacity; the anterior chamber appeared deep centrally, but was not seen peripherally. Therapy including intravenous osmotic agents failed, and on Feb. 6, a trephine filtering procedure was performed. The left eye remained normotensive without therapy. Six months after the operation, visual acuity was R.E.: no light perception, and L.E.: 20/40. The right cornea had an irregular, surface lipid deposition, no filtration bleb was present, and intraocular pressure was R.E.: 71 mm Hg, and L.E.: 8 mm Hg. Repeat ERG showed no response in either eye.

The patient, stable for five more years, presented May 17, 1974, with acute left eye pain, visual acuity of light perception, and intraocular pressure of 65 mm Hg with bullous keratopathy. The anterior chamber appeared peripherally shallow, and gonioscopic examination was impossible. The pressure remained elevated despite a regimen of osmotic agents, acetazolamide, and pilocarpine, and on May 19, we performed a trabeculectomy. Postoperatively, a filtering bleb was present, but pilocarpine 1%, four times daily, was necessary to maintain pressure below 20 mm Hg. Visual acuity improved only to hand motions after operation. With clearing of corneal edema, the peripheral cornea appeared nearly twice the normal thickness, with its posterior surface close to the peripheral iris.

Case 2—This 44-year-old woman, the sister of Patient 1, was first examined in 1964 with a history of poor night vision of eleven years' duration. Visual acuity was R.E.: 20/50, +5.00 +1.00 ×90; and L.E.: 20/40, +6.50. The corneas had ground-glass stromal opacities (peripheral greater than central) similar to Case 1. Intraocular pressure in each eye was 17 mm Hg (Schiøtz), the anterior chamber was of normal depth centrally (gonioscopy impossible), and the fundus was normal. Examination and perimetry studies were largely precluded by poor cooperation. The x-ray films and clinical findings confirmed the diagnosis of Scheie's syndrome.

On July 18, 1970, the patient presented with right eye pain and nausea of three days' duration; right visual acuity was light perception; right intraocular pressure, 50 mm Hg (Schiøtz); severe bullous keratopathy; right pupil measuring 2.5 mm, left pupil, 3.5 mm; narrow anterior chambers; and visual fields in each eye full to V_4 test object (Goldmann). Intraocular pressure decreased to 22 mm Hg after a regimen of pilocarpine, acetazolamide, and oral glycerin; on July 20, we performed a Scheie filtering operation on the right eye. On July 19, we had placed the left eye on pilocarpine 2%, four times daily, when intraocular pressure was 20 mm Hg; on July 27, intraocular pressure suddenly

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rose to 60 mm Hg, immediately leading to peripheral iridectomy in this eye.

Postoperatively, intraocular pressure was R.E.: 17 mm Hg, and L.E.: 21 mm Hg with no therapy, although no bleb was seen on the right eye. Visual acuity was R.E.: hand motions, and L.E.: 20/50. On April 26, 1971, increased intraocular pressure in both eyes was controlled with pilocarpine 4% to attain pressure of 16 mm Hg. The patient had been stable for more than three years in June 1974; visual acuity was R.E.: 20/300, and L.E.: 20/60; pressure in both eyes was controlled below 20 mm Hg with pilocarpine 4%.

Results

Corneoscleral limbus specimens (two from Case 1) and iris specimens (two from each patient) were processed routinely for light microscopy, embedded in paraffin, and stained with hematoxylin and eosin, PAS, toluidine blue, colloidal iron with and without hyaluronidase, and Alcian blue.

Corneoscleral limbus—In these specimens, we saw only scleral collagenous lamellae with a few fibroblasts. No definite trabecular meshwork was identified, although Descemet's membrane was seen on one specimen. Stains for AMP (colloidal iron and Alcian blue) showed much extracellular AMP not sensitive to hyaluronidase, without gross distortion of the connective tissue.

Iris—The four iris specimens showed no visible abnormalities; each had moderate artifactitious folding and distortion. While iris stroma stained positively for AMP, it seemed no more pronounced than in normal iris. The iris stroma was not thicker than normal. There were no pathologic changes in iris pigment epithelium.

Discussion

The clinical management of these two patients was complicated by our inability to evaluate their angles gonioscopically. In analyzing the mechanism of their glaucoma, we must utilize other histologic and clinical findings. Their acute glaucoma resembled angle closure as in each eye sudden elevated intraocular pressures developed unilaterally with a peripherally shallow anterior chamber. Both patients might have had typical angle-closure glaucoma attacks, unrelated to their systemic MPS. The continued ocular hypertension after surgery could have been due to the formation of peripheral anterior synechiae. The uveitis seen in one right eye (Case 1) was probably secondary to prolonged, elevated pressure, and no keratic precipitates were seen in the other three eyes during attacks.

Some aspects of this glaucoma, however, suggest a possible etiologic role for systemic MPS. The patient's brother[2] presently of comparable age, has normal angles, no evidence of glaucoma, and no MPS. Corneal thickening also could have contributed to outflow obstruction. Though the limbal and iris tissue obtained from these patients does not support a hypothesis of angle obstruction by corneal thickening, the limbal specimens showed excessive AMP deposits. Previous ocular histopathologic reports in systemic MPS diseases[6,7] have shown cornea and sclera thickened by AMP deposition. Abnormally thickened anterior segment structures (cornea, sclera, and iris) could conceivably lead to physical obstruction of the angle. Glaucoma has not been previously reported in MPS. Due to systemic complications, few MPS patients with significant corneal clouding (Hurler and Maroteaux-Lamy types) ever reach middle age. Possibly it is only the combination of corneoscleral thickening and angle narrowing with age that provide the substrate for the acute glaucoma in MPS I-S patients with their near-normal life span. While angle obstruction by abnormal limbal AMP storage is a speculative mechanism, we feel it deserves consideration.

A final possible mechanism is obstruction to outflow within the angle by abnormal AMP deposits, without appositional angle closure. The role of hyaluronidase-sensitive AMP in trabecular outflow resistance has been controversial since the initial reports.[8-13] The AMP deposited in MPS I-S (and the other MPS diseases) is, however, hyaluronidase-resistant. Furthermore, such

a mechanism would more likely give rise to chronic rather than acute glaucoma as seen in our patients.

Summary

Two siblings, a 56-year-old white man and a 44-year-old white woman, with systemic mucopolysaccharidosis I-S (Scheie's syndrome) developed acute glaucoma successively in each eye. Their management was complicated by an inability to visualize the anterior chamber angle due to corneal clouding by acid mucopolysaccharide (AMP) deposition. The mechanism of their glaucoma resembled angle closure, which may have been related to thickening of anterior ocular structures due to abnormal AMP storage.

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CEROID LIPOFUSCINOSIS

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Neurolipidosis is a broad term describing neuronal storage diseases that are classifiable into two biochemical groups.

1. The sphingolipidoses (Niemann-Pick disease, Tay-Sachs disease, other atypical GM_2 gangliosidoses, generalized gangliosidosis [GM_1], Gaucher's disease, Krabbe's disease, Fabry's disease, and metachromatic leukodystrophy) are lysosomal metabolism disorders involving conjugated derivatives of ceramide and phospholipid or sugars.[1] Specific catabolic enzyme deficiencies are responsible for the undue accumulation of normal cell constituents. The disorders are hereditary and demonstration of the enzyme deficiency makes it possible to detect heterozygotes (carriers) in order to provide informed prenatal counseling.

2. The nonglycolipid neuronal storage diseases, or ceroid lipofuscinoses (infantile, late infantile, juvenile, adult, and atypical forms), are lysosomal storage diseases involving the accumulation of insoluble fluorescent lipopigments.[2] The responsible biochemical defects are unknown and, except in the instances of late infantile and juvenile variants, recognition of the carrier state is not possible.

We present ten cases of ceroid lipofuscinosis, including infantile, late infantile, juvenile, and atypical variants, and review these disorders that have been grouped under amaurotic familial idiocies or cerebroretinal degenerations.[3]

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SUBJECTS AND METHODS

Of the ten patients with ceroid lipofuscinosis (Table 1), two patients (Cases 4 and 5) who represented atypical juvenile variants with normal visual function have been described previously.[4] All patients underwent complete neurologic evaluation including psychologic testing and electroencephalography (EEG). We performed complete blood cell counts and biochemistry examinations including liver function tests. Bone marrow samples were obtained in all patients and skin biopsy specimens in several. Brain biopsy tissue was examined from either the patients (Cases 3-5, 9, and 10) or deceased siblings with the disorder.

Ocular examination included fundus photography and electroretinography (Figs. 1 and 2). Electroretinograms were performed with a Grass PS 22 photostimulator, 10 inches from the eye, presenting a stimulus target size of 30 degrees. Ping-Pong diffusing spheres were used to produce ganzfeld illumination. The corneal potential was detected with a Lovac Henkes-type contact lens electrode filled with methylcellulose. The signal was processed by a high gain alternating current EEG amplifier coupler with a band pass of 0.1 to 1.0 kHz and common-mode rejection of 80 dB. An ink writing polygraph was used to record the data with simultaneous viewing on an oscilliscope with P7 phosphor and delay line. Photopic tracings were obtained with S2W, S16W, and S16W flicker at 30 per second with ambient illumination of 60 foot candles. Scotopic tracings after ten minutes of dark adaptation were obtained with S1W, S1B, S16W and, when applicable, with a red profile of S1R, S4R, S16R stimuli using Grass filters.

TABLE 1

SALIENT FEATURES OF 10 REPORTED CASES OF CEROID LIPOFUSCINOSIS

Case No.*	Age, yrs	Visual Acuity, Both Eyes†	Ocular Diagnosis	Age at Onset	Presenting Signs	Neurologic Signs
1	17	HM	Exotropia, retinitis pigmentosa	6	Visual acuity loss	Dementia, psychosis, dystonia
2	15	HM	Exotropia, retinitis pigmentosa	6	Visual acuity loss	
3	3½	LP	Severe myopia, retinitis pigmentosa, esotropia	Newborn	Seizures	Seizures, chorea, flaccidity
4	8	20/30	Hyperopia	6	Clumsiness, speech difficulty	Slurred speech chorea
5	10	20/50	Hyperopia	6	Speech difficulty, poor balance	Seizures, dementia, chorea
6	13	LP	Exotropia, retinitis pigmentosa	8	Visual acuity loss	Seizures
7	10	LP	Exotropia, retinitis pigmentosa	5	Visual acuity loss	Neurologically normal, EEG abnormal
8	16	LP	Exotropia, retinitis pigmentosa	5	Visual acuity loss	Seizures, ataxia, dementia
9	6	20/400	Protan red green color defect, inverse retinitis pigmentosa	4	Visual acuity loss	Neurologically normal, EEG abnormal
10	16	LP	Retinitis pigmentosa	4	Visual acuity loss	Seizures

* The following patients were siblings: Cases 1 and 2; Cases 4 and 5; Cases 6, 7, and 8; and Cases 9 and 10.
† HM indicates hand movements; LP, light perception.

DISCUSSION

Ceroid lipofuscinosis is a descriptive term coined by Zeman and associates[2] for a group of neurolipid storage disorders where insoluble fluorescent lipopigments collect in association with membranous intracellular inclusions of various descriptions. The detailed biochemistry of these disorders is unknown and the classification summarized in Table 2 is tentative and descriptive.

These disorders are important to the ophthalmologist because, in the infantile and juvenile forms especially, the presenting sign is decreased visual acuity.[2,5,6] This occurs before other neurologic symptoms are evident. These children often see an ophthalmologist who identifies the disease as hereditary macular degeneration. The possibility of a neurologic disease may be overlooked. Since these disorders are recessively inherited, the family history may be noncontributory and several siblings in one generation can be involved. As with many apparently localized macular degenerations, electrophysiologic studies reveal a more widespread retinal abnormality involving rod function. A pediatric

TABLE 2

TENTATIVE AND DESCRIPTIVE CLASSIFICATION OF CEROID LIPOFUSCINOSIS

Age at Onset	Neurologic Signs	Visual Disturbance	Pathologic Findings
Infantile, under 2 yr	Psychomotor deterioration, ataxia, hypotonia, myoclonus	Severe early visual acuity loss, tapetoretinal degeneration	Granular autofluorescent deposits, severe neuronal loss and brain atrophy
Late infantile, 2–5 yrs (Bielschowsky-Jansky disease)	Seizures, dementia, myoclonus, motor signs	Visual acuity loss, macular changes, tapetoretinal degeneration, optic atrophy	Curvilinear inclusions
Juvenile, 6–8 yr (Batten-Spielmeyer Vogt-Sjögren)	Late motor signs, late seizure and intellectual deterioration, chronic course	Early visual acuity loss, macular changes, tapetoretinal degeneration	Fingerprint patterns, curvilinear inclusions, zebra bodies, lipofuscin bodies, pleomorphic inclusion
Adult (Kufs' disease)	Cerebellar and extrapyramidal signs	Normal visual acuity	Lipofuscin bodies
Atypical, onset at various ages	Cerebellar and extrapyramidal signs	Normal visual acuity	Lipofuscin bodies

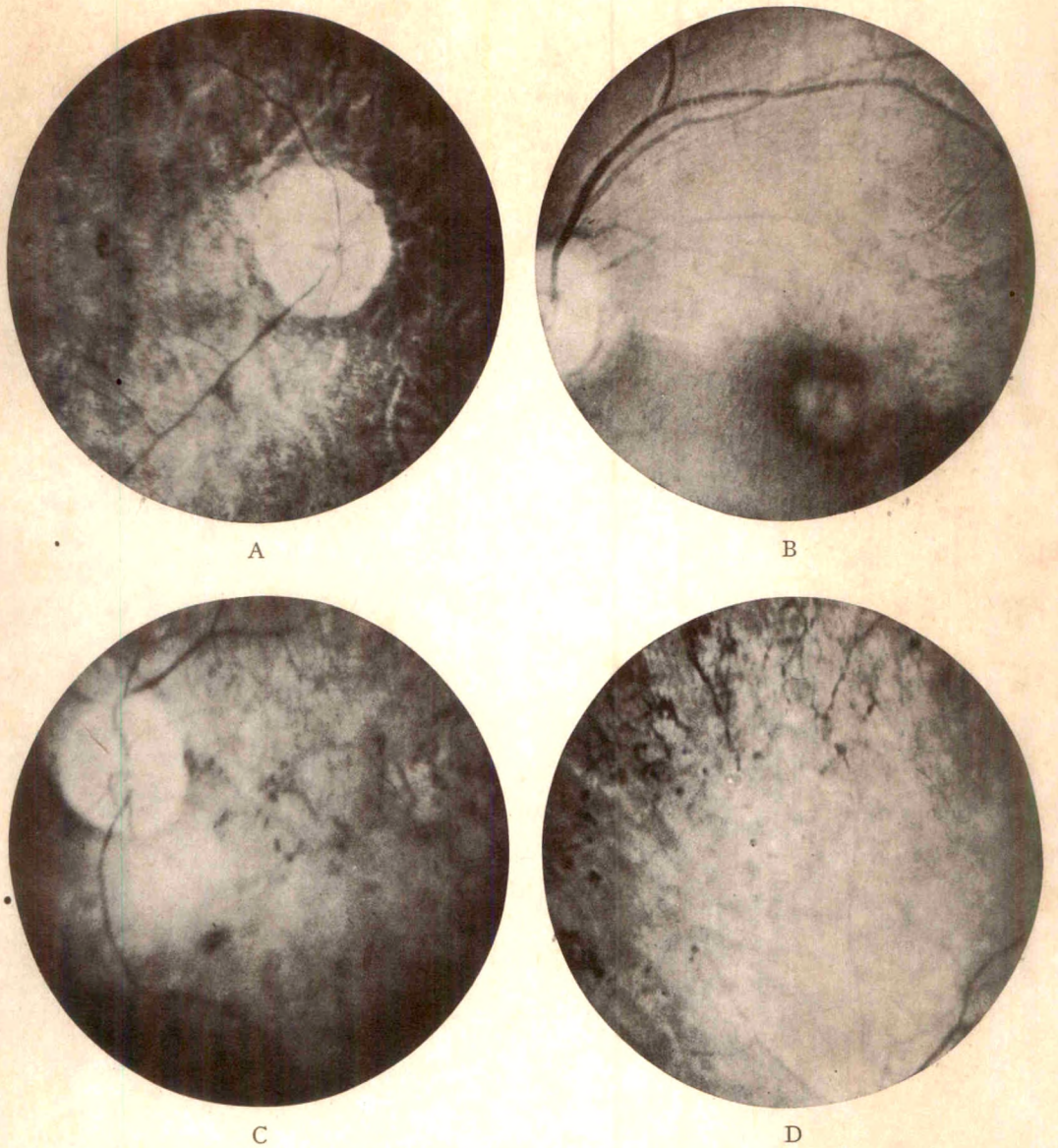
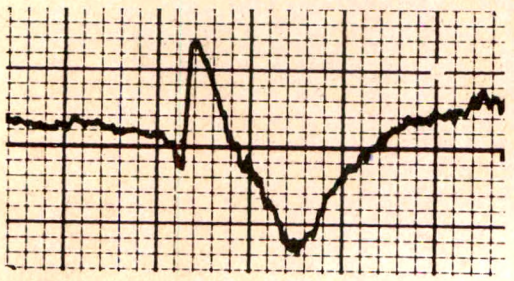


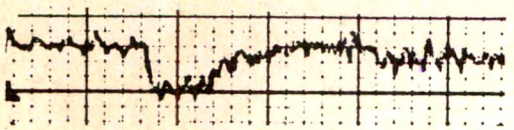
Fig. 1 (Beckerman and Rapin). A, Case 1. Severe pigmentary retinopathy with narrowed vessels and optic atrophy. B, Case 9. Perimacular pigmentation and slight vessel narrowing. C, Case 10. Older sibling of another patient (Case 9) with severe vessel narrowing and diffuse pigmentary disturbance with peripheral corpuscular pigmentation not present in younger sibling (D).

neurologic examination with accompanying EEG studies may reveal evidence of cerebral dysfunction. A peripheral blood smear or a bone marrow sample, or both, may demonstrate azurophilic hypergranulation of the neutrophils in the late infantile form and vacuolated lymphocytes in the juvenile form.[7] The parents and other siblings carrying the abnormal gene may show these changes in their white blood cells and a simple blood test can reveal which family members may be susceptible to the disease. Such carrier identification is not possible for the infantile, adult, and atypical forms.

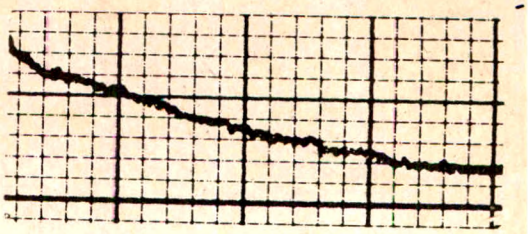
Pathologic studies revealed pleomorphic intracellular inclusions thought to be lyso-



A

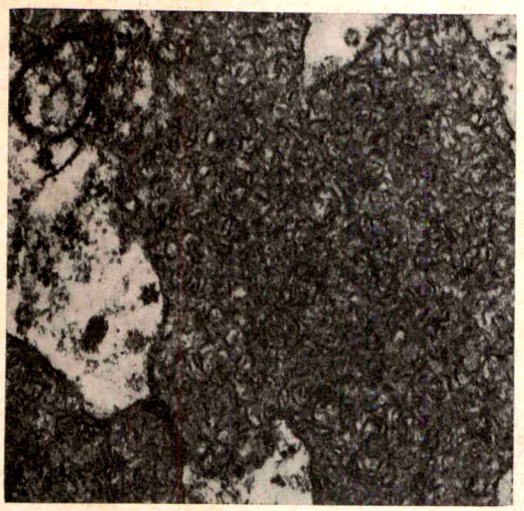


B



C

Fig. 2 (Beckerman and Rapin). Scotopic responses to S1 blue (Grass). A, Case 4. Normal tracing. B, Case 9. Reduced scotopic b-wave amplitude with prolonged implicit time. C, Case 10. Extinguished response.





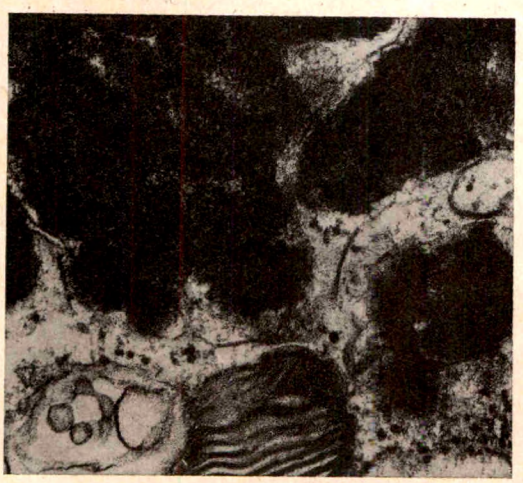


Fig. 3 (Beckerman and Rapin). Top left, Multilamellar or curvilinear bodies in neurons (×40,000). Top right, Fingerprint pattern seen in neuronal inclusion (×61,000). Bottom, Inclusions consisting of dense aggregates of electron-dense material. An inclusion with lamellar structures is also present (×53,000).

somal derivatives in many tissues.[2,4] These inclusions have some tentative value in classifying these disorders (Table 2, Fig. 3). Both retinal and extraretinal ocular tissues show pathologic inclusions.[8,9] A conspicuous decrease or absence of acidic mucopolysaccharides accompanies photoreceptor and pigment epithelial degeneration.[8] Brain biopsy tissue gives the most definitive diagnostic information. No treatment is available for these disorders.

Summary

Seven of ten patients with ceroid lipofuscinosis, including infantile, late infantile, juvenile, and atypical variants, presented with visual acuity loss. In the infantile case visual acuity loss was early and severe. Two patients with atypical variants did not develop ocular abnormalities. Children presenting with macular degeneration may have more extensive retinal involvement on electrophysiologic testing; neurologic evaluation may rule out the prodromal stages of lipofuscinosis.

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COMPUTERIZED AXIAL TOMOGRAPHY IN THE DETECTION OF ORBITAL SPACE-OCCUPYING LESIONS

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The EMI-Scanner system is a computer-aided x-ray technique designed to produce soft tissue tomograms of the brain.[1,2]

The apparatus can also show soft tissue abnormalities in the orbit and a preliminary evaluation of its application to orbital diagnosis was recorded.[3] Two studies appeared subsequently[4,5]; these authors used the 80 × 80 matrix originally fitted to the machine. Baker and associates[4] recorded only one tumor confined to the orbit and Gawler and associates[5] reported three such cases.

We demonstrated primary orbital lesions in 25 verified cases; lesions with secondary extension to the orbit from adjacent structures in the middle fossa or para nasal sinuses were not included in this study. We used a new fine matrix EMI scan (160 × 160 cells) to examine 16 of these patients while the remainder were scanned with the original coarse matrix machine (80 × 80 cells). The results of these EMI scans were compared with other investigative techniques used on the same patients and the absorption values of the various tumors were recorded.

MATERIALS AND METHODS

Of the 41 patients we examined, 24 had surgical and histologic proof of the location and type of lesion present in the orbit. One other patient with an arteriovenous malformation at the apex of the orbit demonstrated by carotid angiography was included in the series. Of these 25 patients, nine were examined with the original coarse matrix scan and 16 with the fine matrix scan.

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The original EMI-Scanner was regarded as an 80 × 80 matrix area with a cell size of 3 × 3 × 13 mm. The fine scan had a 160 × 160 matrix with a cell size of 1.5 × 1.5 × 13 mm. The last dimension was the thickness of the slice to be scanned and an average x-ray absorption value calculated for each cell or cube of tissue. This value was calculated by scanning the head with a narrow x-ray beam detected by a sodium iodide crystal instead of photographic film, as with conventional radiographs. For each position of the scan, we obtained 240 readings. The x-ray source and detector were then rotated through 1 degree and the scan was repeated. This process of traversing and recording was repeated through 180 degrees so that 43,200 (180 × 240) readings were obtained. The data were analyzed by computer and the absorption values for each cube of tissue cal-

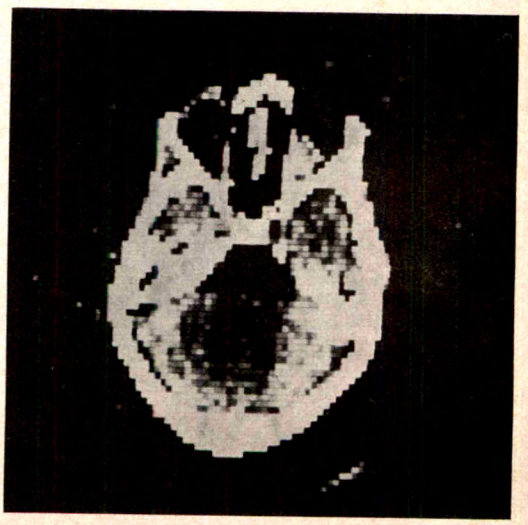


Fig. 1 (Wright, Lloyd, and Ambrose). Case 7. EMI orbital scan (80 × 80 cells) of a 28-year-old woman with an optic nerve meningioma and a tumor mass seen in the apex of the right orbit. The cell size is large and the resolution poor when compared with Figures 2-6.

culated. We retrieved the information either by a numerical printout or by a series of intensity readings on a cathode-ray tube photographed by a Polaroid camera.

Except when contraindicated by a contributory history of sensitivity to iodine-containing contrast media, scans on each patient were repeated immediately after injection of 20 ml of iothalamate sodium 66.8% (Conray 420) to enhance the density of any abnormal tissue and make the differentiation from normal structures easier.

We obtained orbital venograms in all patients, with the frontal vein used for the introduction of the contrast medium. We examined 24 of the patients by axial tomography, a technique previously described and well documented in relation to orbital disease.[6] We examined the affected orbit in all but one of the patients by B-scan ultrasound. A 10-MHz focused transducer with a fast liner scan was employed with water bath ultrasonic coupling.

Results

The EMI scan technique has been shown to yield a high proportion of positive results. In several patients this provided the strongest evidence of abnormality; 21 space-occupying lesions were accurately diagnosed preoperatively (84%). This compared favorably with venography (84%), axial tomography (71%), and ultrasonic examination

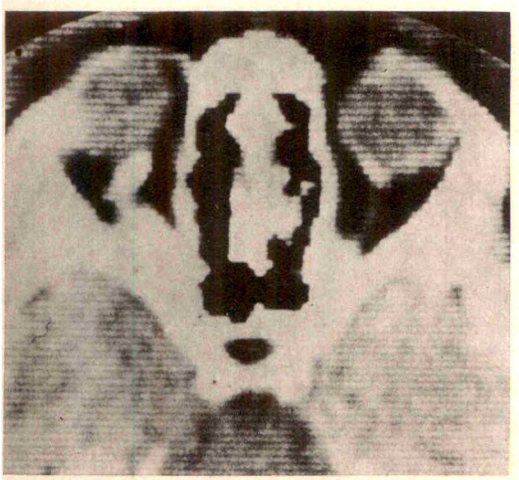


Fig. 2 (Wright, Lloyd, and Ambrose). Case 8. EMI orbital scan (160 × 160 cells) of a 50-year-old woman with primary optic nerve meningioma. A marked thickening of the left optic nerve has a pronounced bulge outward toward the lateral part of the retrobulbar space. The density of the lesion was enhanced after injection of 20 ml of iothalamate sodium 66.8%.

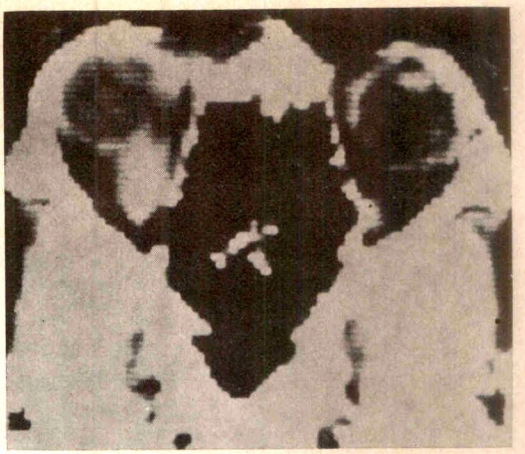


Fig. 3 (Wright, Lloyd, and Ambrose). Case 18. EMI orbital scan (160 × 160 cells) of a 30-year-old man with a primary optic nerve meningioma. An intraconal lesion is seen on the left side; the tumor is closely related to the left optic nerve and extending forward to the posterior aspect of the globe.

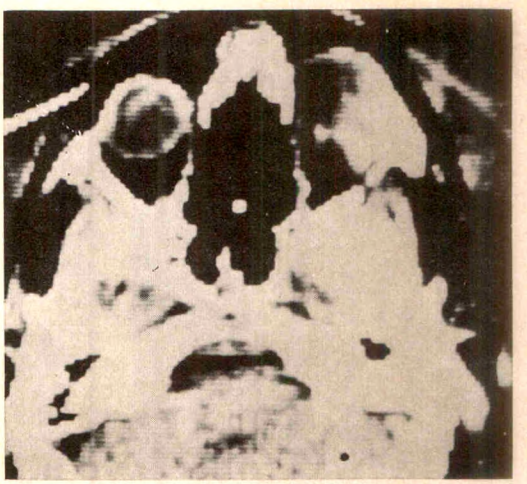


Fig. 4 (Wright, Lloyd, and Ambrose). Case 19. EMI orbital scan (160 × 160 cells) of a 63-year-old man with a squamous cell carcinoma. A tumor mass on the right side is situated laterally and posterior to the globe, corresponding to the situation of the lacrimal gland.

TABLE

COMPARISON OF THE RESULTS IN 25 PATIENTS WHO UNDERWENT SURGICAL EXPLORATIONS OF THE ORBIT*

Case No., Age, Sex	Clinical Presentation	EMI Scan	Orbital Venography	Axial Hypocycloidal Tomography	Ultrasound B-Scan	Verified Diagnosis
1, 49, M	Failing right vision for 1 yr, eye became blind with increasing proptosis during the next 2 yr; R.E.: no light perception, L.E.: 20/20; 22-mm right proptosis; exposure keratitis with perforation of the cornea; cataractous lens	Correct	Correct	Correct	Correct	Malignant melanoma of choroid with extension into the orbit
2, 58, M	3-yr left proptosis; previous surgery to remove an orbital meningioma; R.E.: 20/20, L.E.: light perception; 3-mm left proptosis	Correct	Correct	Correct	Unsuccessful examination	Meningioma
3, 41, M	Left proptosis since childhood; sudden onset of diplopia; R.E.: 20/15, L.E.: 20/30; left 6th nerve palsy; geographic left visual field loss	Correct	Incorrect	Correct	Correct	Arteriovenous malformation
4, 63, M	5-mo blepharoptosis and swelling of the left upper eyelid; 2-mm left proptosis; mass palpable in upper part of orbit	Correct	Correct	—	Correct	Pseudotumor
5, 8, F	6-mo progressive left proptosis; R.E.: 20/20, L.E.: 20/110; 3-mm left proptosis; optic disk edema	Correct	Correct	Correct	Correct	Optic nerve glioma
6, 38, F	Acute left proptosis 18 mo previously with loss of vision, 4 wk gradual diminution in proptosis; immediately prior to surgery, left eye slightly enophthalmic; blind with optic atrophy	Incorrect	Correct	Correct	Incorrect	Resolved granuloma in orbital apex
7, 28, F	6-mo blurred vision in right eye, onset during pregnancy; R.E.: light perception below, L.E.: 20/20; 4-mm right proptosis with chronic edema of the optic disk	Correct	Correct	Correct	Correct	Primary optic nerve meningioma
8, 50, F	Gradual deterioration of vision in left eye for 3 yr; 2-mm left proptosis with optic atrophy	Correct	Correct	Correct	Correct	Optic nerve meningioma
9, 14, F	8-mo blurred left vision and diplopia; R.E.: 20/200 amblyopic, L.E.: 20/60; 4-mm left proptosis displaced down 3 mm; hard mass lacrimal fossa	Correct	Correct	Correct	Incorrect	Adenocarcinoma of lacrimal gland
10, 30, M	6-mo double vision with swelling of the left lower eyelid; R.E.: 20/15, L.E.: 20/15; left globe proptosed 3 mm, displaced upward 2 mm	Correct	Correct	Incorrect	Incorrect	Orbital pseudotumor
11, 37, F	2-yr vision obscuration in left eye, gradually increasing in frequency and severity; R.E.: 20/20, L.E.: 20/30; 2-mm left proptosis; left chronic disk edema	Incorrect	Incorrect	Incorrect	Correct	Cystic hygroma of optic nerve
12, 41, F	12-mo right blepharoptosis and diplopia; right eye proptosed; R.E.: 20/60 amblyopic, L.E.: 20/30; 5-mm right proptosis	Correct	Correct	Correct	Correct	Neurilemmoma
13, 34, F	18-mo progressive left proptosis; R.E.: 20/20, L.E.: 20/20; 5-mm left proptosis	Correct	Correct	Correct	Correct	Cavernous hemangioma

* The accuracy of each examination was assessed by the indication for or against surgery.

TABLE (*Continued*)

Case No., Age, Sex	Clinical Presentation	EMI Scan	Orbital Venography	Axial Hypocycloidal Tomography	Ultrasound B-Scan	Verified Diagnosis
14, 38, M	4-yr progressive right proptosis with diplopia on upgaze; R.E.: 20/20, L.E.: 20/20; 8-mm right proptosis	Correct	Incorrect	Incorrect	Correct	Intraconal lymphoma
15, 56, M	Blind right eye for 2 yr; 12-mo progressive proptosis; disorganized globe; R.E.: no light perception, L.E.: 20/20	Unsuccessful examination	Incorrect	Correct	Correct	Malignant melanoma of choroid
16, 21, F	6-mo swelling of right upper eyelid; mass in lacrimal fossa; right globe displaced downward 5 mm and forward 3 mm	Correct	Correct	Correct	Incorrect	Benign mixed cell tumor of lacrimal gland
17, 37, M	Obscuration of right vision 3 yr before when looking to the right with chronic disk edema; previous orbitotomy to decompress optic nerve; gradual deterioration of vision in right eye; R.E.: light perception, L.E.: 20/20; 3-mm right proptosis	Incorrect	Correct	Incorrect	Incorrect	Primary optic nerve meningioma
18, 30, M	Blurred left vision for 9 mo; 6-mo progressive left proptosis; R.E.: 20/15, L.E: 20/40; obscurations of left vision when looking to the left; left chronic disk edema with retinal striae	Correct	Correct	Correct	Correct	Primary optic nerve meningioma
19, 63, M	3-mo history of swelling of the right upper eyelid; 4-wk blurring and distorted vision with pain in the right eyebrow; occasional diplopia; R.E.: hand movements, L.E.: 20/30; large tender mass in upper outer quadrant of right orbit, indenting globe	Correct	Correct	Correct	Correct	Squamous cell carcinoma probably originating in a dermoid cyst
20, 52, F	12-mo progressive right proptosis; firm mass in upper outer quadrant of right orbit; 8-mm proptosis, displaced down 4 mm	Correct	Correct	Correct	Correct	Lacrimal gland carcinoma
21, 59, M	2-yr painless progressive right proptosis; large soft mass in upper outer and both lower quadrants of the orbit with extension onto cheek; 11-mm proptosis	Correct	Correct	Incorrect	Correct	Lymphoma
22, 77, M	1-yr progressive right proptosis; diplopia for 6 mo; globe displaced forward 6 mm and downward 6 mm; no mass palpable; horizontal choroidal striae at posterior pole	Correct	Correct	Incorrect	Correct	Benign mixed cell tumor of lacrimal gland
23, 69, F	8-mo right proptosis, double vision when looking upward; mass in upper outer quadrant of orbit; 4-mm proptosis, displaced down 5 mm and nasally 3 mm; horizontal choroidal striae at posterior pole	Correct	Correct	Correct	Correct	Malignant change in a mixed cell tumor of the lacrimal gland
24, 32, F	12-mo progressive deterioration of left vision; R.E.: 20/20, L.E.: 20/200; 2-mm left axial proptosis; left optic disk edematous, choroidal folds at macula	Correct	Correct	Correct	Correct	Intraconal cavernous hemangioma
25, 42, F	18-mo blurred right vision with noticeable 12-mo proptosis; R.E.: 20/30, L.E.: 20/15; 3-mm right proptosis; choroidal folds at posterior pole	Correct	Correct	Incorrect	Correct	Cavernous hemangioma

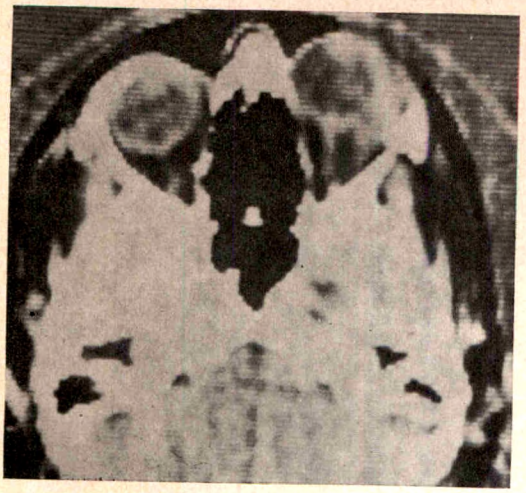


Fig. 5 (Wright, Lloyd, and Ambrose). Case 20. EMI orbital scan (160 × 160 cells) of a 52-year-old woman with an undifferentiated lacrimal gland carcinoma. A markedly proptosed right eye with a dense lesion is situated laterally extending backward and slightly behind the globe.

(76%) in the same group of patients. We used a combination of these techniques to obtain a completely successful preoperative diagnosis in all patients (Table). During the period in which these patients were examined, a program using a larger 160 × 160 matrix was fitted to the EMI scanner. With this larger matrix, the cell size was reduced to 1.5 × 1.5 × 13 mm, resulting in a substantial improvement in the scan with much better visualization of normal orbital structures (compare Figure 1 with Figures 2-6). The outline of the globe, rectus muscles, and optic nerve were clearly visualized and abnormal soft tissue structures more clearly defined. This modification has enormously increased the diagnostic potential of the apparatus as far as the orbit is concerned, and probably some of the earlier diagnostic errors (Cases 6 and 11) would have been avoided if the smaller matrix had been available. However, we made the third diagnostic error using the fine matrix scanning system (Case 17). The fine matrix was used to examine 16 patients, giving a preoperative diagnostic rate of 93%, a significant improvement on the original system.

The results we obtained using the high resolution scan showed the increased reliability of the apparatus; an example of its diagnostic potential was seen in one patient (Case 14). A 38-year-old man presented with proptosis that had been investigated three years previously with inconclusive results and a provisional diagnosis of dysthyroid exophthalmos. When we examined him, orbital venography and axial hypocycloidal tomography were normal. However, an ultrasonic B-scan showed a mass immediately behind the globe and an EMI scan concurred. In this case, the decision to explore the orbit was based on the EMI scan. A lateral orbitotomy was performed and a retrobulbar lymphoma (23 × 20 mm) was found adherent to the globe and optic nerve immediately behind the macula, with the short posterior ciliary vessels adherent to its capsule. The lesion responded well to radiotherapy with complete resolution of the proptosis.

While the results of the EMI scans were generally excellent, we missed the orbital lesions in two patients and made a false diag-

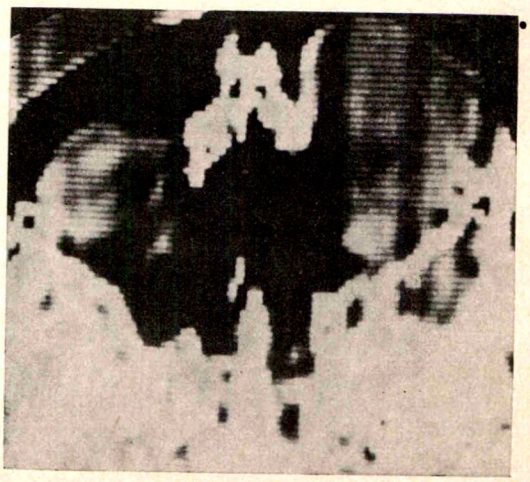


Fig. 6 (Wright, Lloyd, and Ambrose). Case 1. EMI orbital scan (160 × 160 cells) of a 49-year-old man with a malignant melanoma of the choroid extending into the orbit. A large retrobulbar mass in the right orbit is continuous with the globe anteriorly and reaching almost to the bony apex of the orbit posteriorly.

nosis in a third case suggested by venography, history, and clinical signs. The first false-negative diagnosis was made using the larger matrix scanner (Case 11), an example of the value of ultrasonic examination. The patient, a 37-year-old woman, noticed obscurations of vision in her left eye for two years. At first the visual acuity loss was noted when she straightened up after bending forward and it lasted for about ten seconds. Gradually the obscurations increased in both frequency and duration and occurred without any change of posture. She had a fields were normal, with visual acuity of chronic edema of the optic disk. Her visual fields were normal with visual acuity of R.E.: 20/20, and L.E.: 20/30. A neurosurgical unit could not diagnose the cause of the choked disk. When seen in the orbital clinic, she had no abnormalities by axial hypocycloidal tomography and orbital venography showed a venous obstruction at the superior orbital fissure. However, an ultrasonic B-scan showed enlargement of the anterior portion of the optic nerve. The EMI scan showed a normal orbit. Because of the information provided by an ultrasonic scan and the worsening of the patients' symptoms, we explored the optic nerve through a lateral orbitotomy. At surgery the anterior portion of the optic nerve was grossly enlarged (diameter, 8 mm). Incision of the nerve sheath released a large quantity of cerebrospinal fluid, revealing a cystic hygroma of the optic nerve.[7]

The other false-negative diagnosis with the fine matrix EMI-Scanner was made in a patient with a recurrent meningioma of the optic nerve (Case 17). The patient, a 40-year-old man, noticed transient episodes of visual acuity loss in his right eye when he looked to the right. The right eye was slightly proptosed with chronic edema of the optic disk. Visual acuity was 20/20 in both eyes when he looked straight ahead but his right eye became blind on attempting dextroversion. Fluorescein angiography showed that when he looked to the right, blood flow through the central retinal artery ceased. The optic nerve was approached through a lateral orbitotomy and a fibrous primary meningioma of the optic nerve was found involving the anterior 2 cm of the nerve. Total removal of the meningioma would have caused complete loss of vision. Therefore, the nerve was decompressed by excising the meningiomatous tissue from the lower temporal quadrant of the sheath. Further compression of the optic nerve eventually produced complete loss of vision, and the patient was admitted for removal of the meningioma. An EMI scan showed scar tissue from previous surgery in the lateral part of the orbit with no demonstrable abnormality within the muscle cone. However, when the nerve was exposed through a lateral orbitotomy it was diffusely enlarged by further growth of the meningioma (diameter of the nerve and sheath, 7 mm).

The only false-positive EMI scan diagnosis was made using the large matrix scanner (Case 6). The patient initially developed severe proptosis with accompanying loss of vision. The proptosis gradually resolved during the ensuing eight months. When the patient was first seen in the clinic six months after the commencement of symptoms, the affected eye was proptosed 1 mm with marked optic atrophy and visual acuity was reduced to vague light perception. A provisional diagnosis of a previous acute orbital apex syndrome caused by a pseudotumor was made. The diagnosis was further strengthened by the venographic findings of obstruction of the third part of the superior orbital vein in the orbital apex and the development of slight enophthalmos during the ensuing months. However, an EMI scan and ultrasonic B-scan showed a mass in the orbit suggesting the presence of a meningioma of the optic nerve. On the basis of these two investigations, we explored the orbit and residual fibrous tissue was found in relation to the optic nerve at operation, histologically resembling a resolving granuloma or pseudotumor.

The average x-ray absorption values, recorded by numerical printout from the computer, were within the 22 to 28 range. The meningiomas recorded up to 100% enhancement of the density values after intravenously administered iothalamate sodium 66.8%, compared with an increase of 16 to 33% density enhancement in the remaining tumors and pseudotumors. Based on our experience of intracranial tumors, neurilemmomas should show a degree of contrast enhancement similar to the meningiomata, but this was not verified for the orbit.

Discussion

The EMI-Scanner is an accurate new method of investigating orbital disease. Modification of the original scanner by fitting a new matrix improved the resolution and increased the diagnostic potential of the method, which is noninvasive and consistently outlines small soft tissue masses. In several cases, the EMI-Scanner provided the main evidence of abnormality. However, it is not infallible and should be used as a complimentary procedure to other noninvasive methods, such as axial hypocycloidal tomography and ultrasound. Furthermore, it does not replace current radiologic methods of examining lesions that have invaded the orbit from the paranasal sinuses or the adjacent bones. Gawler and associates,[5] who described ten patients with orbital disease, recorded only four lesions wholly confined to the orbit. The remaining six patients had an orbital extension of a disease process arising in an adjacent structure, which could have been diagnosed by radiographs and hypocycloidal tomography. In the same context, the diagnosis of pseudoproptosis caused by unilateral myopia can be made more accurately with ultrasound. We also showed that orbital venography is still required when investigating suspected orbital tumors, and carotid angiography is a necessary procedure in some patients, particularly those with suspected vascular anomalies in the orbit.

Summary

Of 41 patients we examined for a suspected primary orbital tumor, 25 patients had evidence of a lesion either histologically, angiographically, or surgically. We examined nine of the 25 patients by means of an EMI-Scanner and 16 by a fine matrix addition (160 × 160 cells), and compared these results to those we received by axial tomography, orbital venography, and B-scan ultrasound. We also compared the absorption values of the recorded tumors. The EMI-Scanner had a diagnostic accuracy of 84%; orbital venography, 84%; axial hypocycloidal tomography, 71%; and ultrasound, 76%. The fine matrix scanner gave a preoperative diagnostic rate of 93% and defined optic nerve abnormalities accurately. However, EMI scanning should complement existing noninvasive procedures and orbital venography.

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SUDDEN ONSET OF BILATERAL SYMMETRICAL PROPTOSIS IN ACUTE INTRACRANIAL HYPERTENSION

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Sudden onset of bilateral symmetrical proptosis, a rare clinical condition, results from a symmetrical increase in the intraorbital contents. Although malignant exophthalmos, due to generalized deposition of hydrophilic mucopolysaccharide in the orbits, is generally bilateral, its onset is gradual. According to Duke-Elder and Scott,[1] bilateral symmetrical proptosis may develop suddenly in a subarachnoid hemorrhage from a ruptured intracranial aneurysm. It is probably caused by venous congestion in the orbit, resulting from intracranial hypertension.

CASE REPORT

A 32-year-old man presented on July 24, 1974, with an eight-month history of early morning vomiting and intense left frontal headache of one month's duration. During recent months, vomiting had increased to two or three times daily. The headache had persisted day and night for two weeks. One week before admission, there was a blood-stained, loose stool. There was no history of fits, visual disturbances, or head injury. He had been treated for cervical tuberculous adenitis for one year.

Examination elsewhere showed full consciousness and noncontributing neurologic signs. Tests for typhoid and infectious hepatitis were negative. On July 27, the patient became confused and drowsy. Examination disclosed bilateral partial sixth cranial nerve palsy. The left pupil was larger than the right but both pupils reacted briskly to light.

In order to exclude tuberculous meningitis, a lumbar puncture was done after infusing 200 ml of 10% mannitol solution. The xanthochromic cerebrospinal fluid had a pressure of 160 mm H_2O, containing 10 lymphocyte cells/mm^3; protein was 10 mg/100 ml; and glucose, 53 mg/100 ml. There was a free rise and fall of fluid during the Queckenstedt's sign. The acid-fast stain was negative.

After the lumbar puncture, the patient became stuporous, the left pupil became dilated and fixed, respiration became stertorous and periodic, and the plantar responses became extensor. During the next few hours, both eyes became proptosed.

On admission here, the patient was unconscious with total left hemiplegia, a left-sided, widely dilated and fixed pupil, obvious bilateral proptosis with conjunctival chemosis, and edematous eyelids. The optic disks were edematous. Exophthalmometric readings, taken in the supine position, were R.E.: 28 mm, and L.E.: 29 mm.

There was no vertical or horizontal displacement of the eyes, which were nonpulsatile and could be pressed back easily into the orbits without resistance. The right arm and leg moved and responded to painful stimuli but the left arm and leg exhibited only decerebrate postures. Blood pressure was 160/90 mm Hg, the pulse rate was 70 beats per minute, and the temperature was 36.7°C.

In view of the left-sided, dilated, fixed pupil, the ipsilateral hemiplegia, and a history of left-sided headaches, the diagnosis was chronic subdural hematoma. The left hemiplegia was considered to be a false localizing sign. We believed that the sudden deterioration of consciousness and the development of other neurologic signs were the result of acute tentorial coning after the lumbar puncture. Plain radiographs of the skull taken elsewhere were noncontributory.

We infused 350 ml of 20% mannitol solution for a short period before cerebral angiography and surgery. The carotid angiogram (Figure) confirmed the presence of a giant left-sided, subdural hematoma that was evacuated through the posterior parietal and frontal burr holes. The subdural blood was liquid and of varying colors, presumably due to its long duration. After evacuation of the hematoma, we found that the surface of the hemisphere was 4 cm deep to the dura mater in the frontal region.

Seven postoperative subdural taps were done at increasing time intervals. The aspirated fluid decreased in each successive tap, and no fluid was aspirated on the last occasion. The shift of the midline structures was assessed by serial echo encephalograms.

On the day after surgery, the patient moved his left arm and leg but developed a right-sided total hemiplegia. Four days after the operation, the patient was conscious but aphasic. One week after the operation there was improvement in the proptosis, which virtually disappeared by the middle of the second week.

During the third week, the patient spoke several words and movement had returned to the right arm and leg. He then made steady progress. By the fifth week, right facial weakness had almost dis-

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Figure (Choudhury). Left carotid angiogram. Anteroposterior view of the late arterial phase, showing the subdural hematoma and a marked shift of the anterior cerebral artery to the right.

appeared. The patient walked with support and his speech was greatly improved. Ten weeks later, he had virtually recovered. There were no unusual neurologic signs and the exophthalmometric readings were R.E.: 19 mm, and L.E.: 18 mm.

Discussion

A history of vomiting and increasingly severe headaches indicated the presence of increased intracranial pressure. The traditional view is that lumbar puncture is contraindicated in the presence of papilledema. However, papilledema often may be absent in intracranial hypertension, and careful consideration should be given before performing lumbar puncture in any patient with possible hypertension.

Lumbar puncture performed elsewhere in our patient precipitated acute tentorial coning. A consequence of temporal lobe hernia is displacement of the midbrain toward the opposite side, compressing the opposite cerebral peduncle against the sharp edge of the tentorium, and causing ipsilateral hemiplegia. Acute tentorial coning probably resulted in further aggravation of the intracranial hypertension which, in turn, produced increased intracranial venous pressure.

The increased intracranial venous pressure was transmitted from the intracranial cavity to the orbital veins, resulting in orbital venous stasis and the sudden onset of bilateral proptosis. Subsequent venous congestion and edema of the orbital tissues then caused progression and a further increase in the intraorbital contents. Bilateral symmetrical proptosis then resulted. The gradual disappearance of the proptosis after release of the intracranial hypertension supports this hypothesis.

The superior and inferior ophthalmic veins in the orbit drain the posterior orbit and empty into the cavernous sinus while the frontal, nasal, and anterior facial veins drain the anterior orbit and empty into the common facial vein. The two systems communicate freely; they also communicate through the pterygoid venous plexus. In addition, absence of valves in these venous systems provides an alternative drainage between them.

With such free communication, venous stasis due to increased intracranial venous pressure that produces proptosis is unusual. However, reports that noninflammatory lesions near the cavernous sinus produce ipsilateral proptosis attest to the inadequacy of anterior orbital venous drainage. Dixon[2] and Meadows[3] described cases of exophthalmos due to pituitary adenomas. Aneurysms near Willis' circle may produce similar changes, presumably by the same mechanism.[2,4] However, because venous stasis develops slowly in these conditions, proptosis is gradual.

Association of hemorrhage into the extraocular orbital tissues and optic nerve sheath was reported in cases of sudden intracranial hypertension.[5,6] This factor may contribute to minor degrees of bilateral proptosis but it does not explain the presence of such

extraocular congestive features as conjunctival chemosis and edematous eyelids, the absence of any visual disturbances, and the occurrence of bilateral gross symmetrical proptosis.

Summary

A 32-year-old man had the clinical features of progressive increase in intracranial pressure due to a chronic subdural hematoma except for papilledema. Lumbar puncture, however, precipitated acute tentorial coning and severe neurologic signs. The tentorial coning resulted in an acute aggravation of intracranial hypertension and precipitated an increase in the intracranial venous pressure that was transmitted to the orbital veins, causing orbital venous stasis, symmetrical increase in the intraorbital contents, and symmetrical bilateral proptosis.

Acknowledgments

I thank J. C. Taylor, F.R.C.S., for permission to report this case, and R. Whitaker, F.F.R., for permission to reproduce the radiograph.

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Ophthalmic miniature

"... Where did it go to?"
"We don't know, miss."
Harriet looked at the stout and agitated Carrie, whose face was puckered and twitching and her eyes bolting with imminent hysteria. She had never thought the present head scout any too dependable, and was inclined to put down her abundant energy to an excess of thyroid.

Dorothy L. Sayers
Gaudy Night

RETINAL CRYOPROBE IN ORBITAL TUMOR MANAGEMENT

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Henderson[1] described a method for removing orbital tumors by applying a cryoprobe to them. We have found that this method is valuable in the surgical management of orbital and ocular adnexal tumors.

We used the retinal cryoprobe to exert moderate traction on orbital tumors, facilitating biopsy or removal. The cryoprobe can also be used to seal and to assist in the removal of ruptured orbital cysts.

We also found that tumors retained their microscopic structure after application of the cryoprobe, thereby allowing histopathologic diagnosis.

CASE REPORTS

Case 1—A 6-year-old white girl had had the appearance of a "small right eye" for seven months that was actually proptosis of the left eye; it had been particularly noticeable for four days prior to our first examination of her in November 1973.

Visual acuity was R.E.: 20/20, and L.E.: 20/30. There was slight limitation in abduction and elevation of the left eye. The left pupil was 1 mm larger than the right and had a Marcus-Gunn response. The left optic disk margin was blurred, with one flame-shaped hemorrhage nearby. The left eye was 5.5 mm proptotic and was 2 mm below the level of the right eye. A slight resistance occurred in retrodisplacing the left eye. Perimetric tests showed an enlarged blind spot on the left.

Optic foramen x-ray views revealed an optic canal, 7 mm in diameter, on the right side and an 8-mm canal on the left. Pneumoencephalography was normal, and showed no evidence of abnormality in the optic chiasm. Optic nerve glioma was suspected, but because we lacked documentation and had a variety of different opinions regarding management of this disease,[2] we explored the orbit for histologic confirmation.

In December 1973, the patient underwent a modified Krönlein orbitotomy[3] of the left orbit. The optic nerve, strikingly enlarged from the globe to the optic foramen, was about 10 mm in diameter, and was covered by a thick plexus of sinusoidal blood vessels. Traction with the adherent cryoprobe allowed withdrawal of the nerve

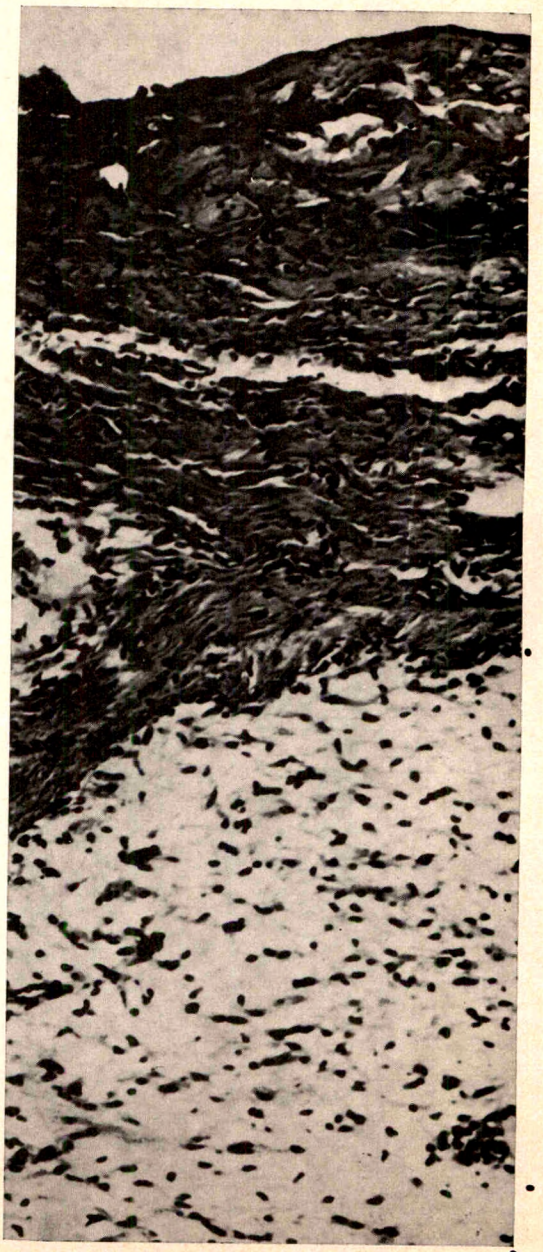


Fig. 1 (Putterman and Goldberg). Case 1. Characteristic structure of optic glioma is unaltered by cryoprobe application (×250).

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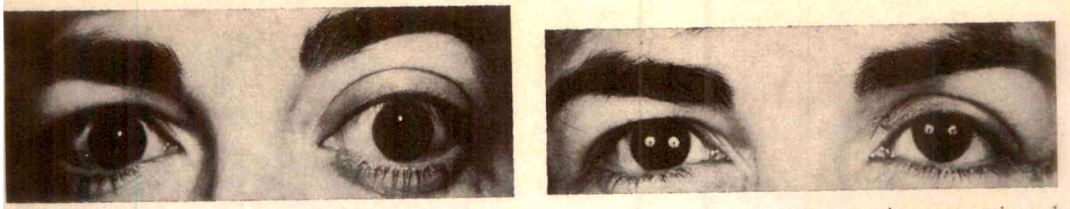


Fig. 2 (Putterman and Goldberg). Case 2. Left, Preoperative photograph demonstrating proptosis and depression of left eye. Right, Postoperative photograph after Krönlein orbitotomy excision of left orbital cavernous hemangioma.

into the operative field and excision of the ice ball (containing dura mater and peripheral optic nerve) without application of forceps or clamps. We cut one specimen from the area, 2 × 2 × 2 mm, prepared it for frozen section examination, and examined a 4- × 4-mm section extending 2 to 3 mm into the mass histopathologically. No significant bleeding occurred. The frozen and conventional sections revealed an optic glioma, whose characteristic microscopic appearance was not changed by the cryoprobe application (Fig. 1). Because preoperative visual function was almost normal, we elected not to excise the nerve.[2]

Postoperatively, visual acuity was L.E.: 20/100. The blind spot, amaurotic pupillary response, the peripheral field, and the proptosis were unchanged.

Case 2—Since 1968 this 36-year-old white woman has had loss of visual acuity in the left eye (Fig. 2, left). Since 1969, there has been proptosis on the left. Multiple orbital and systemic examinations revealed no apparent cause, and a trial course of systemic corticosteroids decreased the proptosis but was discontinued due to intolerable side effects.

We first examined the patient in April 1974. Visual acuity was R.E.: 20/20, and L.E.: 20/400. There was 8 mm of left proptosis, and ocular motility of the left eye was restricted in upgaze. The left pupil reacted sluggishly to light and accommodation, was 2 mm wider than the right, and showed a Marcus-Gunn response. The temporal aspect of the left optic disk was pale. There was complete loss of the left temporal field.

Conventional and tomographic x-ray films and optic foramen views showed an increased density of the posterior medial orbital wall. An orbital scan revealed diffuse uptake in the entire left orbit. Orbital venography and carotid arteriography demonstrated a tumor in the muscle cone.

On May 15, we explored the left orbit through a modified Krönlein orbitotomy approach[3] and found a large, firm, spherical mass behind the left eye in the muscle cone. The mass, purplish and smooth, extended to all four walls as well as to the orbital apex. The tumor enveloped the optic nerve and displaced it against the medial orbital wall. The retinal cryoprobe applied to the tumor allowed firm traction once the ice ball formed (Fig. 3, left). Blunt dissection with a fingertip and cotton-tipped applicator freed the tumor from the surrounding tissue. The cryoprobe was repetitively defrosted and placed on the tumor in a progressive circumferential direction in order to apply traction in all directions and to assist in freeing the tumor from adhesions to orbital tissues. The tumor, removed within its capsule, measured 2.5 × 1.5 cm (Fig. 3, right).

Microscopic sections revealed the tumor to be

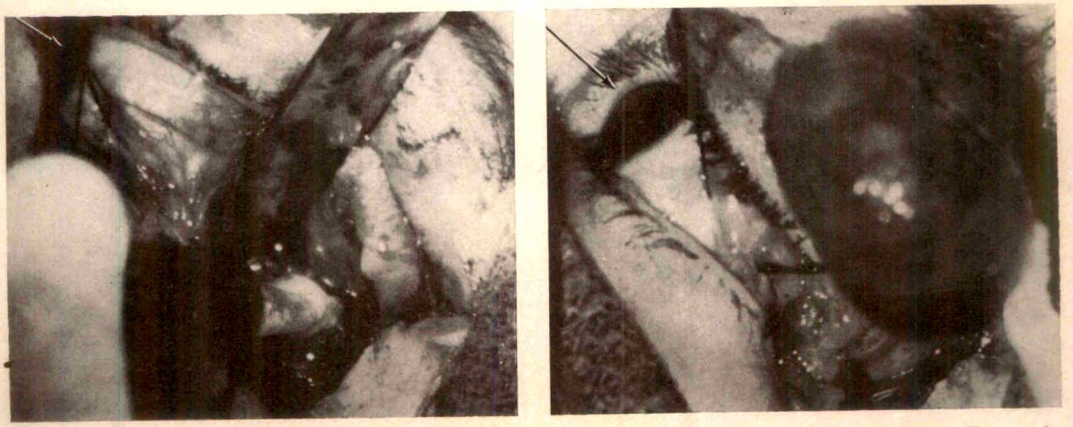


Fig. 3 (Putterman and Goldberg). Case 2. Left, Cryoprobe applied to hemangioma. Right, Cryoprobe allowed moderate traction to be applied to the tumor, facilitating its intracapsular removal. Arrows indicate corneas.



Fig. 4 (Putterman and Goldberg). Case 2. Characteristic structure of cavernous hemangioma is unchanged despite repetitive cryoprobe applications (×250).

an orbital cavernous hemangioma, unaltered by the multiple, prolonged cryoprobe applications (Fig. 4).

The patient had an uneventful postoperative course and in July, visual acuity was 20/20 with a full peripheral field of vision in the left eye (Fig. 2, right). Ocular motility returned to normal. Her appearance was acceptable, with no signs of either proptosis or enophthalmos. Pallor of the temporal optic disk persisted.

Case 3—A 30-year-old black man suffered a gunshot wound to the right side of his face in 1970, with subsequent loss of vision in his right eye. Several months after this injury, he noted swelling over the left medial canthal area. In April 1974, he had a 13- × 20-mm subcutaneous, movable cystic mass nasal to the left medial canthus.

In July, the mass was removed. The skin was vertically incised nasal to the mass, and blunt dissection isolated the nasal side of the cyst. We applied moderate traction to the wall of the cyst with the retinal cryoprobe, while blunt and sharp dissection released the inferior aspect of the cyst from the surrounding tissue. The cryoprobe was then replaced in a more inferior aspect of the cyst wall and the inferotemporal cyst wall was bluntly dissected from the surrounding tissue. During dissection the anterior portion of the cyst wall was adherent to the skin and tore slightly, leading to a discharge from the created opening. To prevent the cyst wall from collapsing, we applied the cryoprobe over the opening, sealing it with an ice ball. We freed the rest of the cyst wall from the skin and removed it intact.

The mass was an epidermoid cyst containing a gunshot pellet and keratin. Microscopic examination revealed that cryoprobe applications had not disturbed the cyst wall (Fig. 5). Postoperatively, the patient was asymptomatic with a normal cosmetic appearance.

Case 4—A 44-year-old white man had intermittent painful loss of vision and proptosis of his left eye for one month and diplopia for two days.

Visual acuity was R.E.: 20/20, and L.E.: 20/30. The left eye was proptosed 6 mm, was hypertropic, and had limitation in depression. There were choroidal folds and discedema in the left eye. A perimetric test revealed an enlarged blind spot in the left eye. An orbital scan demonstrated a diffuse, increased uptake in the left orbit and ultrasonography revealed an orbital mass. Orbital venography and carotid arteriography revealed a



Fig. 5 (Putterman and Goldberg). Case 3. Epidermoid cyst containing keratin. Arrow indicates site of gunshot pellet. Application of cryoprobe to ruptured cyst sealed opening and allowed removal in entirety. Characteristic structure of cyst was unaltered by cryoprobe application (original magnification, ×50).

2- × 3-cm vascular tumor in the left muscle cone.

A left Krönlein orbitotomy[3] revealed a large spherical mass in the muscle cone that extended to all four orbital walls and from the globe to the apex of the orbit: It was covered by several large blood vessels and was firmly adherent to the surrounding tissue. The retinal cryoprobe, applied to the lateral aspect of the tumor, provided moderate traction while blunt dissection with the fingertip and cotton-tipped applicator separated the tumor from surrounding tissue. We repeatedly applied the cryoprobe in a circumferential direction around the tumor as the tumor was progressively separated from the adherent tissue. When about one half of the tumor had been freed from the surrounding tissue, we applied moderate traction to the tumor with the cryoprobe to free a tight adhesion to superior tissues. This led to rupture of the tumor capsule. Residual tumor and part of the capsule were easily expressed from the muscle cone by blunt dissection with the fingertip. The remaining portion of the tumor capsule was not removed, because rupture of the capsule had increased the risk of damaging orbital structures.

Microscopic sections revealed that the tumor was a benign orbital hemangiopericytoma, unaltered by the multiple prolonged cryoprobe applications (Fig. 6).

Two months postoperatively, the patient's visual acuity was 20/25, with normal motility and no signs of proptosis.

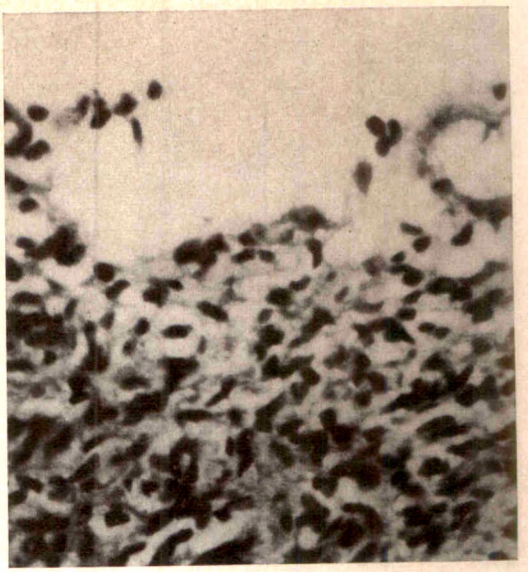


Fig. 6 (Putterman and Goldberg). Case 4. Hemangiopericytoma. The capsule of the tumor ruptured when we applied marked traction with the cryoprobe to separate tight adhesions between the tumor and surrounding tissue (×250).

Discussion

We used the retinal cryoprobe in one patient (Case 1) to apply traction to the optic nerve without tearing it. It was not necessary to place toothed forceps or clamps into the substance of the nerve. The traction also facilitated the recovery of frozen and conventional histopathologic specimens. There was no significant bleeding from the sites of tumor removal. In Case 2, we were able to apply moderate traction to the hemangioma without tearing its capsule; the cryoprobe also aided in intracapsular delivery. Progressive circumferential reapplication of the cryoprobe tip along the course of blunt dissection of the tumor was an advantageous method of removing the tumor. In Case 3, we were able to exert more pressure on the cyst wall with a cryoprobe application than with forceps or clamps. The progressive circumferential reapplication used in Case 2 was valuable in this case also. When the cyst was severed, we sealed the opening with the cryoprobe and removed the cyst in its entirety, decreasing the risk of reoccurrence. In Case 4, we applied moderate traction to the hemangiopericytoma with the circumferential reapplication of the cryoprobe, facilitating separation of about one half of the tumor from surrounding tissue. However, when we applied marked traction to the tumor to separate tight adhesions to the superior orbital tissues, the capsule ruptured. This demonstrates that use of the cryoprobe is not without potential complication. However, grasping the tumor with forceps or other instruments would have caused rupture of the capsule with much less traction than that induced with the cryoprobe. Certain tumors, including hemangiopericytomas,[4] are friable and rupture more easily than others.

In all four cases, the cryoprobe application had no apparent effect on the microscopic details of the histopathologic sections.

Summary

We used the retinal cryoprobe in the surgical management (biopsy and excision) of

orbital and ocular adnexal tumors in four patients. The strong bond between the cryoprobe tip and the tumor allowed application of moderate traction to the tumors, facilitating their removal. The amount of traction on the tumor or cyst appeared to be much greater than that caused by forceps or clamps. In one case, however, marked traction with the cryoprobe caused rupture of the tumor capsule. In another case, in which a cyst wall was entered during dissection, we applied the cryoprobe to the opening, sealing the hole with an ice ball, to keep the cyst from collapsing.

Histopathologic structure was not altered by cryoprobe applications.

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Ophthalmic miniature

The fallacy of analogy: This is based on a resemblance among different categories of things. When the relationship among A and B resembles the relationship between X and Y, at some point it is argued that other relationships between A and B will also be true for X and Y. The analogy may be of use in suggesting relationships but has no validity as proof unless there is similarity rather than limited resemblance. An example is that this or that plan or organization cannot be changed because "you can't unscramble eggs." Another example is, "Where there's smoke, there's fire."

"You can draw water out of a water-well," said the Hatter, "so I should think you could draw treacle out of a treacle-well—eh, stupid?"

Dwight J. Ingle
Fallacies and errors in the Wonderlands
of Biology, Medicine, and Lewis Carroll
Perspectives in Biology and Medicine
15:258, 1972

POLYCYTHEMIA VERA ASSOCIATED WITH USHER'S SYNDROME

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Usher's syndrome is a hereditary disorder characterized by congenital deafness and progressive blindness known as retinitis pigmentosa.[1,2] It is frequently associated with a variety of congenital-hereditary disorders such as loss of olfactory and gustatory sensitivities, aphasia, mental retardation, abnormal electroencephalogram (EEG) findings, psychiatric disturbances, myoclonic epilepsy, and vestibular dysfunction.[2,3] It may also be part of several of the following rare congenital degenerative syndromes: Cockayne's syndrome[4,5] characterized by retinitis pigmentosa, mental retardation, dwarfism, and nerve deafness; Hallgren's syndrome[6] characterized by retinitis pigmentosa, vestibulocerebellar ataxia, and nerve deafness; Laurence-Moon-Biedl syndrome[7] characterized by pigmentosa, mental retardation, obesity, polydactyly, hypogonadism, and nerve deafness; Refsum's disease[8] characterized by retinitis pigmentosa, polyneuritis, ichthyosis, and nerve deafness. The association of hereditary nephritis with nerve deafness (Alport's syndrome)[9] and hereditary nephritis with retinitis pigmentosa[10] were also reported.

Although there were several early reports of familial polycythemia,[11,12] the role of heredity has not been demonstrated in the etiopathogenesis of polycythemia vera.

We describe the association of Usher's syndrome and polycythemia vera in a 50-year-old man.

CASE REPORT

A 50-year-old man was hospitalized on March 13, 1974, with the chief complaints of redness of the face, hands, and feet, perspiration of one year's duration, and fasting epigastric pain of three months' duration. He had congenital deafness and initially had failing vision at the age of 30 with severe headaches and dizziness. Although visual acuity became progressively worse and he continued to suffer from headaches and dizziness, he worked as a manual laborer until his present complaints started.

The family history revealed three members of his family with congenital deafness and progressive blindness (Figure). There was no consanguinity in the family. The 34-year-old sister of the propositus and two daughters of the paternal aunt of the propositus, aged 22 and 14, had congenital deafness and developed failing vision at an earlier age. No other member of the family was reported to have redness of the face and body. One son, the only family member available for examination, had normal blood values and no ocular or auricular abnormalities.

The patient was a well-developed man with striking redness of the face, especially in the lips, cheeks, nose, ears, neck, hands, and feet. He was deaf and his visual fields were extremely narrow. He had a labile high blood pressure, occasionally fluctuating between 160/100 and 130/80 mm Hg. His spleen was palpable, four fingers-breadth below the left costal margin. The remainder of the physical examination was within normal limits.

We compiled his hematologic findings (Table). Urinalyses were normal. Intravenous pyelograms did not reveal any renal pathologic findings. Tests for syphilis showed negative results. Skull and chest x-ray films were within normal limits. Electroencephalograms were normal.

Ophthalmologic examination revealed characteristic findings of retinitis pigmentosa. Examination showed retinal atrophy, pallor of the optic disk, and pigmented areas encroaching near the optic disk and macula. Visual fields were constricted in both eyes; only a small central area of vision remained. Examination of the ears revealed bilateral sensoneural hearing loss. Olfactory and gustatory sensitivities were normal. Aphasia, mental retardation, and psychiatric disturbances were not present. The remainder of the neurologic examination was within normal limits.

DISCUSSION

The diagnosis of polycythemia vera in this patient was confirmed by the finding of increased red cell mass, normal arterial blood oxygen percent saturation, splenomegaly, and an elevated leukocyte alkaline phosphatase level.[13,14] Polycythemia vera is a relatively uncommon disease. The annual incidence

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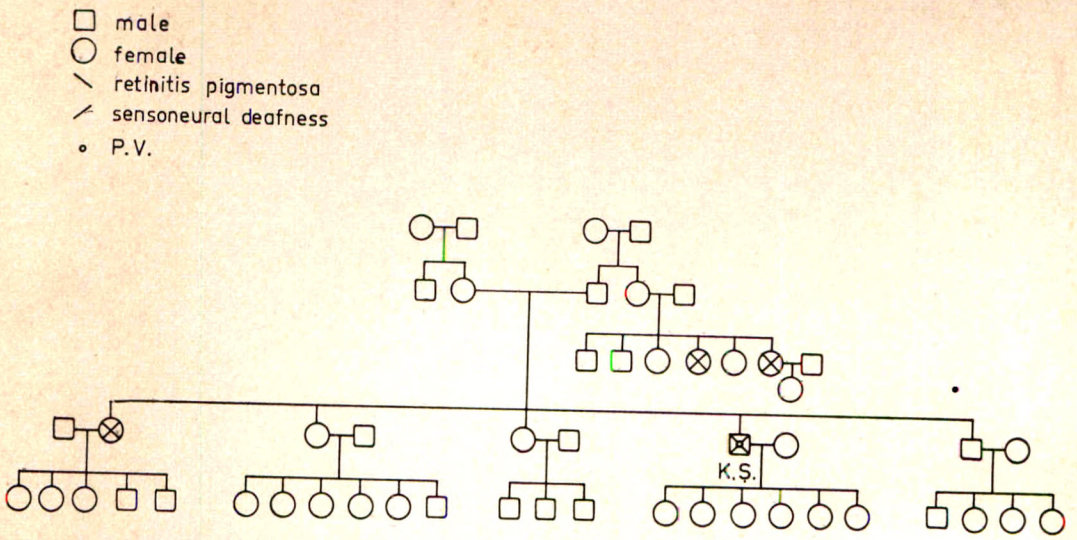


Figure (Müftüoğlu, Akman, and Savaş). Family pedigree.

rate was reported to be four to five new cases per million population in the Baltimore area.[15] Usher's syndrome is also rare, occurring in three cases per 100,000 population.[2] The association of two uncommon diseases in the same patient warrants consideration of a common pathogenetic mechanism. Many previous case reports described erythrocytosis in patients with various disorders of the brain and autonomic nervous system.[16–18] These cases of neurogenic polycythemia were thought to be caused by an excessive stimulation of the hypothalamus and the pituitary gland.[18,19] The association

TABLE

HEMATOLOGIC DATA

Test	Values
Erythrocytes	6,120,000 mm³
Hemoglobin level	20 g/100 ml
Hematocrit value	68%
Leukocytes	7,000–9,200/mm³
Differential cell count	Within normal limits
Platelets	370,000/mm³
Sedimentation rate	3 mm/hr
Bone marrow aspiration	Mild erythroid hyperplasia
Bone marrow biopsy	Hyperplastic marrow with a shift to the left in erythroid series
Fallout (escape) phenomenon*	60% (normal, 20–40%)
Hemoglobin electrophoresis (starch-gel)	No abnormal hemoglobins
Arterial blood oxygen percent saturation	100%
Venous blood oxygen percent saturation	82%
Total erythrocyte volume	53.37 ml/kg (normal, 36 ml/kg for men)
Leukocyte serum alkaline phosphatase	220 units/100 ml (normal, 8–20)
Chromosome analysis	Normal karyotype (46, XY)
Blood histamine level	Not increased
Platelet aggregation	
With adenosine diphosphate	Defective
With adrenalin	Defective

* This phenomenon refers to the many untrapped red blood cells after clot retraction in polycythemia vera.[22]

of polycythemia with cerebellar hemangioblastoma was also reported.[20] In the latter condition, the pathogenesis of polycythemia seems to be related to the over-production of erythropoietin.[20] Whatever the pathogenetic mechanisms are, none of the patients fulfilled the criteria for the diagnosis of polycythemia vera.[16-20] Neuropsychiatric examination including skull x-ray films and EEG did not reveal other nervous system disorders in our patient. Lack of clinical history, normal urinalyses and intravenous pyelograms also ruled out hereditary nephritis and nephrogenic polycythemia.[9,10,21] Polycythemia has not been linked to various syndromes associated with either nerve deafness or retinitis pigmentosa.[1-3] Usher's syndrome was present in four members of the patient's family. Polycythemia vera was diagnosed in only one member of a family carrying this genetic condition. No evidence could be discovered to support more than a chance association between Usher's syndrome and polycythemia vera in this patient. Studies of Usher's syndrome that involve central nervous system degeneration associated with a wide variety of abnormalities may be helpful in shedding light on many of the diseases associated with it.[2]

Summary

A 50-year-old man with Usher's syndrome, progressive retinitis pigmentosa, and congenital sensoneural deafness developed polycythemia vera. Usher's syndrome was associated with a variety of congenital-hereditary disorders but there was no evidence to support more than a chance association between Usher's syndrome and polycythemia vera.

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PATHOGENESIS OF APHAKIC MACULAR EDEMA

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One of the most perplexing problems in ophthalmology is an uneventful cataract extraction with poor visual acuity result due to macular edema with or without papilledema. Irvine[1] described the postoperative development of macular changes with vitreous opacities. He ascribed these findings to the development of vitreous adhesions to the operative wound. Subsequently, several authors[2-7] described loss of vision after cataract extraction due to changes in the optic nerve and macula. The pathogenesis of this syndrome, although attributed to many disorders, remains obscure. This is due in part to the fact that no specimen has been available for histologic examination where the diagnosis was made clinically and confirmed by fluorescein angiography.[8]

We describe a case of cystoid macular edema and papilledema after cataract extraction in which fluorescein angiography was obtained five months postoperatively. The aphakic eye in question, as well as its phakic fellow eye, became available for histopathologic examination one month after the fluorescein study. Evaluation of these specimens suggests a common factor in the different clinical presentations of cystoid macular edema.

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CASE REPORT

A 71-year-old man seen for the first time in May 1973, had progressive, painless loss of vision for three years. Visual acuity was R.E.: counting fingers at 3 feet, and L.E.: 20/100. Retinal function tests were normal. There were dense lenticular opacities in each eye and ophthalmoscopic details could not be seen in the right eye. The left fundus appeared unremarkable. In June the patient underwent an uneventful intracapsular cataract extraction of the right eye. One month postoperatively, visual acuity in the right eye was 20/40 with some vitreous haze. Subsequently, visual acuity decreased to 20/200 over the next three months. In December, a serous detachment of the macula with cystoid macular edema was noted by biomicroscopy.

A fluorescein angiogram showed the typical pattern of cystoid macular edema (Fig. 1). The disk also appeared abnormally hyperfluorescent, but photographs of the left fundus for comparison were not available due to the remaining cataract.

One month after the fluorescein study, the patient was admitted to the hospital for a cerebral vascular accident and died three days later.

RESULTS

The corneal epithelium of the right eye revealed an occasional proliferated cell in the basal layer. A healed surgical incision was found superiorly, anterior to the corneoscleral limbus. A small portion of Descemet's membrane was present within the well-healed wound and lying perpendicular to the angle of the corneal stromal fibers. Only a minimal amount of fibrosis was present at the internal surface of the wound. We saw no vitreous humor in or near the wound. The corneal endothelium showed a decrease in the number of cells. The angle appeared open on each side.

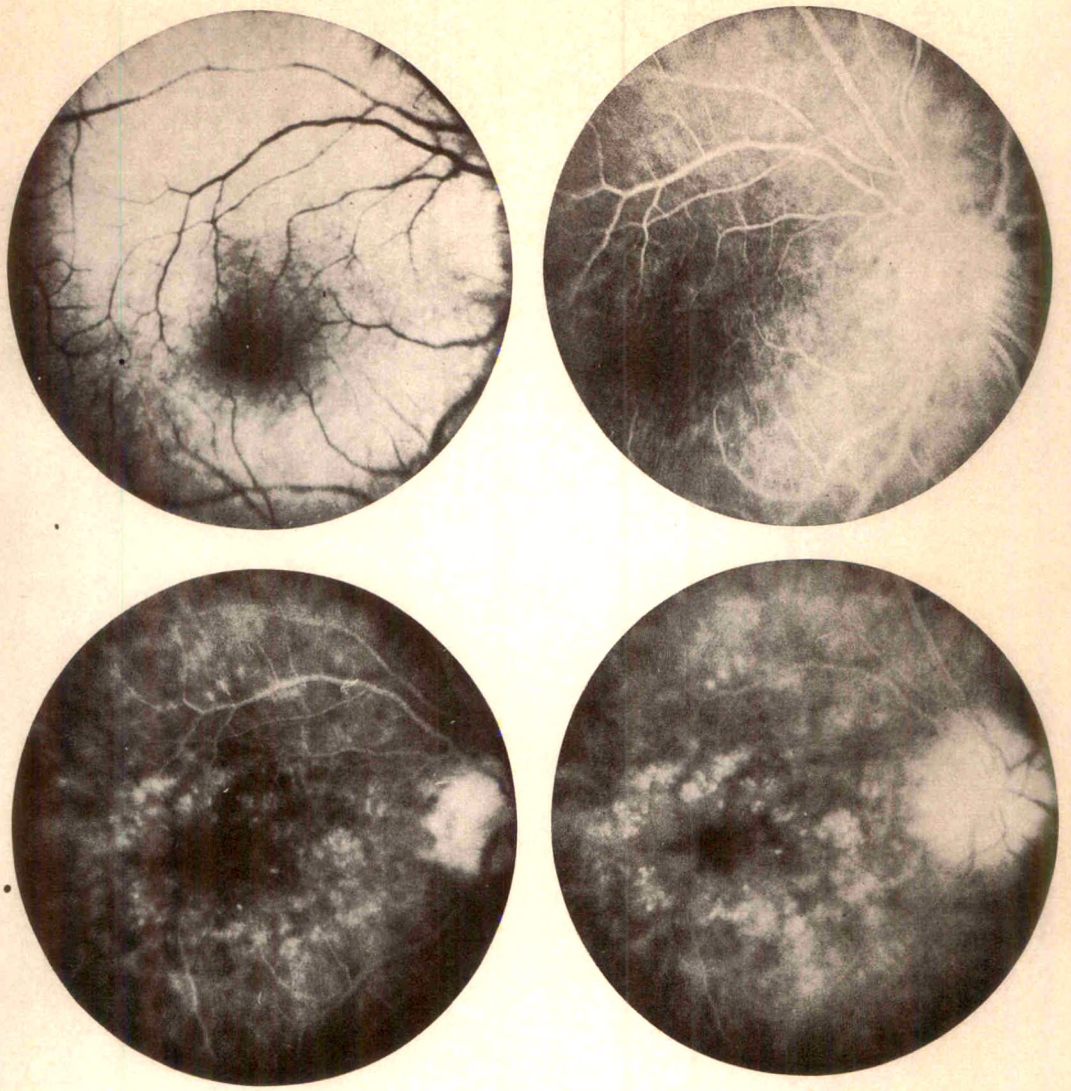


Fig. 1 (Norton and associates). Fluorescein angiography study. Top left, Preinjection photograph. Macular edema and subretinal fluid are visible. Top right, Thirty seconds postinjection, early leakage of dye into perifoveal area. Bottom left, Progressive leakage of fluorescein into macula from perifoveal vessels. Bottom right, Fifteen minutes after dye injection, there is a typical flower-like pattern of macular edema. Note hyperfluorescence of optic disk.

The superior iris limb arched posteriorly at about one half the length of the iris. A vitreous strand was seen at the margin of the iris extending back along the posterior surface (Fig. 2). Picoryl aniline blue stain revealed the strand extending posteriorly back to the region of the pars plana. Scattered round cells were found in the pupillary portions of the superior iris limb. The opposite iris limb did not appear remarkable. The base of the iris and anterior portion of the ciliary body, internal to the ciliary muscle, contained a considerable accumulation of round inflammatory cells (Fig. 3). Some sections showed round cells only in the superior portion while in others the cells were seen in the inferior portion. Still other sections had varying degrees of round cell infiltration on both sides of the ciliary body. This finding suggested an irregular but widespread distribution of the

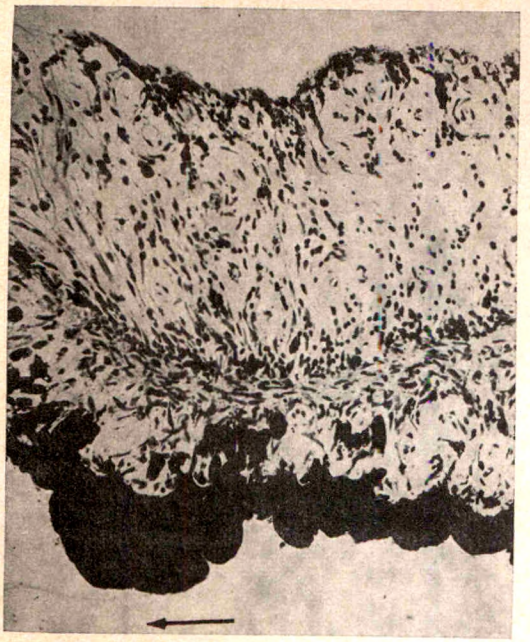


Fig. 2 (Norton and associates). Section of iris reveals round inflammatory cells near pupillary margin. Arrow points to fine adherent vitreous strand (Picoryl aniline blue, ×52).

inflammatory cells. There was peripheral cystic degeneration of the retina. The macular region was locally detached, with granular material separating the neurosensory retina from the pigment epithelium (Fig. 4). Cystic spaces were noted within the neurosensory retina, primarily affecting the outer plexiform and outer nuclear layers. There was some fragmentation of the photoreceptor processes. PAS stain revealed some thinning of the intact internal limiting membrane. The optic nerve head was unremarkable.

The corneal epithelium of the left eye was rough and abraided on the surface. There was some decrease in cells of the endothelial layer. The angle appeared open. One iris limb was artifactitiously broken but the iris was normal in other respects. A few scattered round cells were found in the ciliary body (Fig. 5). The lens showed considerable cortical liquefaction.

The retina showed peripheral cystic de-

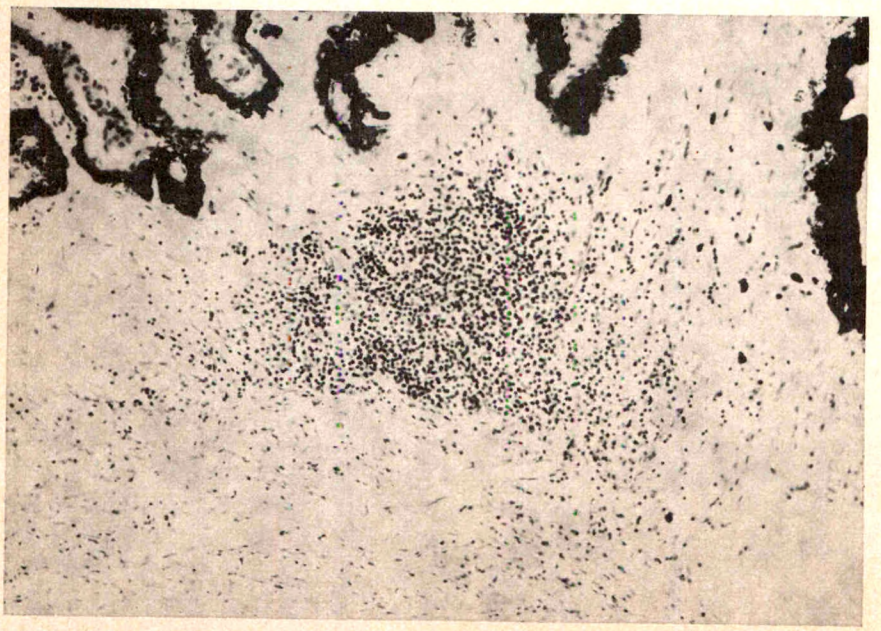


Fig. 3 (Norton and associates). Ciliary body in aphakic eye demonstrates accumulation of chronic inflammatory cells. These are greatest in number internal to the ciliary muscle (hematoxylin and eosin, ×52).

generation. In the macular region, the outer cone processes were irregularly separated from the remainder of the cell due to processing. Postmortem degeneration of the photoreceptor layer was seen in some areas. The optic nerve was not remarkable.

Discussion

In his original description of macular edema following cataract extraction, Irvine[1] suggested that the macular changes were due to remote vitreous traction or secondary to an iritis. Gass and Norton,[9] who presented a thorough study of patients with this syndrome, demonstrated a cystoid collection of fluid in the macula by fluorescein angiography, as well as edema of the optic nerve-head, and suggested that the cause was related to alterations in capillary permeability.

Gass and Norton[9] described one eye studied histopathologically, 21 months after cataract extraction. Although the diagnosis of cystoid macular edema was not made clinically prior to enucleation and the eye was not studied with fluorescein angiography, they believed the diagnosis could be made retrospectively on the basis of the clinical history. Histopathologically, their specimen demonstrated a fine vitreous strand that extended from the pars plana to the well-healed cataract wound, extensive macular cystic changes, and mild glaucomatous alterations in the peripheral retina. Aside from drusen, the choroid and pigment epithelium were normal. No mention was made of ciliary body or iris inflammation.

In our specimen there were two regions with chronic inflammatory changes. One was the sector of iris adherent to a vitreous strand, the other was a generalized patchy ciliary body inflammation. Cystoid macular edema was noted biomicroscopically one month previously, and confirmed by fluorescein angiography. The specimen showed significant cystoid spaces in the neurosensory retina, confined primarily to the macular area. There was some peripheral cystoid degeneration.

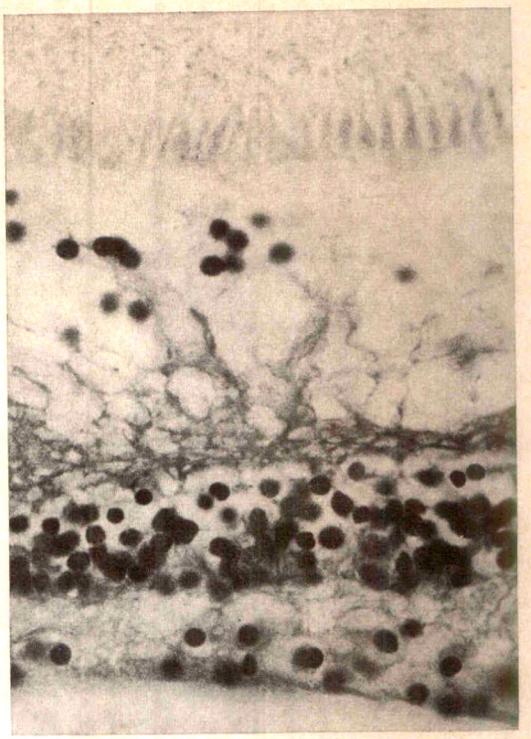


Fig. 4 (Norton and associates). Cystoid macular edema of neurosensory retina in operated aphakic eye. A fine granular material separates pigment epithelium from neurosensory retina. There are cystic spaces primarily in the outer plexiform and outer nuclear layers. There is some fragmentation of the photoreceptor processes. The internal limiting membrane appears slightly thinned, but intact (hematoxylin and eosin, ×52).

Our findings tend to confirm Gass and Norton's[9] suggestion that direct macular traction from vitreous adherence does not play a role in most cases of postcataract extraction macular edema. Rather, ocular inflammation, in conjunction with some deficit in retinal capillary integrity, may be responsible.

A recent report from England supports this hypothesis. In a series of patients undergoing cataract extraction, 50% showed cystoid macular edema six to seven weeks postoperatively.[10] Analysis of predisposing factors to this condition showed that operative trauma with resultant inflammation, to-

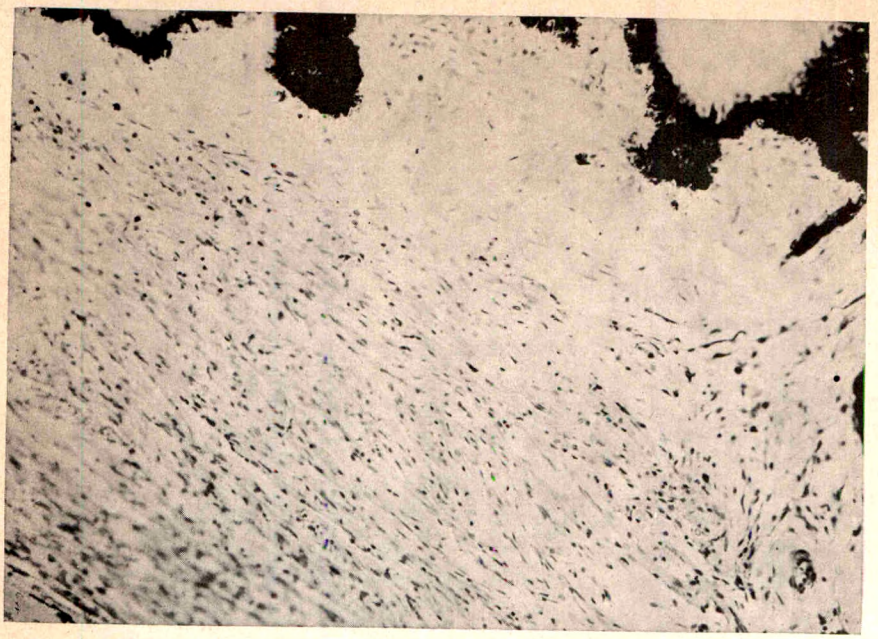


Fig. 5 (Norton and associates). Ciliary body in phakic fellow eye. There are a few scattered round cells (hematoxylin and eosin, ×52).

gether with systemic vascular disease and previous ocular inflammatory disease, played an important role in the pathogenesis.

Another clinical syndrome, pars planitis, consisting of peripheral posterior segment inflammation, vitreous opacities, and macular edema may also be related to postcataract extraction macular edema.[11] Histologic examination of eyes diagnosed clinically as having pars planitis showed organization of the vitreous base, but aside from occasional mononuclear cells in the iris, the uveal tract was free of inflammation.[12] In eyes diagnosed as having recurrent acute cyclitis, there was a similar clinical picture of vitreous opacities, cystoid macular edema, and heightened retinal vascular permeability. In these eyes, extensive ciliary body inflammation or extensive peripheral chorioretinal scars extending into the ciliary body were present.[12]

Based on the available evidence, peripheral uveal tract and especially ciliary body inflammation seems to play an important role in effecting the pathogenesis of cystoid macular edema. The mechanism of this effect must yet be discovered.

Summary

Six months after cataract extraction, a 71-year-old man had cystoid macular edema confirmed by fluorescein angiography. Microscopic examination revealed cystoid spaces in the outer plexiform and outer nuclear layer of the neurosensory retina. Chronic inflammatory cells were scattered throughout the ciliary body. Inflammatory cells were also present in a section of iris that had an adherent strand of vitreous leading to the pars plana. Comparison of these findings with other related clinical entities supported the hypothesis that ciliary body inflammation may play a significant role in postcataract extraction macular edema.

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OPHTHALMIC MINIATURE

The point settled that spectacles are required, the next consideration is to choose them with judgment. Dr. Kitchiner avers that many have no idea that it is requisite to choose at all. They disinter from the buried effects of the last generation a pair of family spectacles, and the older the ancestor who wore them, and the dimmer were his eyes, the greater they suppose must be the virtue of the glasses which enabled him to see. If the practice be indeed common, spectacles ought to be broken over the coffins of their owners, like the wand of office on the grave of royalty.

Spectacles
Quart. Rev.
Vol. 87, 1850

THE INCIDENCE OF RETINAL DETACHMENT AFTER PENETRATING KERATOPLASTY

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The incidence of retinal detachment after cataract extraction is well documented at approximately 2%.[1] However, to our knowledge, no detailed series of penetrating keratoplasties have been studied for this same complication. We present an analysis of a series of 610 penetrating keratoplasties to determine the incidence of retinal detachment following corneal surgery.

METHODS

Charts were reviewed on 485 consecutive patients undergoing penetrating keratoplasty during the period from Jan. 1, 1969, through April 30, 1973. All patients were referred to Shands Teaching Hospital with corneal pathology, which at the time of surgery was severe enough in all but a few cases to preclude ophthalmoscopic evaluation for retinal breaks or early retinal detachment.

RESULTS

The incidence of retinal detachments was subdivided into phakic, aphakic, and combined procedures (penetrating keratoplasty with cataract extraction) (Table 1). The groups were further subdivided into those with and without vitreous manipulation (vitreous manipulation includes use of cellulose sponges, or aspiration of vitreous fluid with a syringe through the pupil, or use of the vitreous suction cutter through the pupil. Cellulose sponges were often used in conjunction with aspiration or with the suction cutter).

Phakic—There were 218 phakic procedures. In only one of these was there vitreous manipulation (aspiration through the pars plana). In this group of phakic keratoplasties there were no retinal detachments.

Aphakic—There were 261 aphakic keratoplasties; 59 were without vitreous manipulation and in these there were no retinal detachments. However, in 202 patients undergoing aphakic keratoplasty associated with anterior vitrectomy, there were ten retinal detachments.

Combined—There were 131 combined procedures performed. In 72 procedures performed without vitreous manipulation, there were no detachments. In 59 procedures performed with vitrectomy, there were four retinal detachments.

DISCUSSION

In 1934, Shapland[2] estimated the incidence of retinal detachment after cataract extraction at 2.2% and almost 40 years later, Scheie, Morse, and Aminlar[1] found an incidence of 2.2%. Vitreous fluid loss during cataract surgery increases the incidence of retinal detachment to about 7%,[3] emphasizing the relationship of vitreous body to retinal detachment. Further evidence of the importance of the vitreous body in the precipitation of retinal detachment in our series is that retinal detachment only occurred after keratoplasty if the vitreous body was manipulated.

Fine,[4] in a series of 209 aphakic keratoplasties, noted five detachments, an incidence of 2.4%. He made no mention of vitreous manipulation. Our overall incidence of detachment in aphakic patients undergoing

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TABLE 1

INCIDENCE OF RETINAL DETACHMENT OCCURRING AFTER PENETRATING KERATOPLASTY

Type of Procedure	No. of Penetrating Keratoplasties	No. of Retinal Detachments	Incidence, %
Phakic keratoplasty	218	0	0
Without vitreous manipulation	217	0	0
With vitreous manipulation	1	0	0
Aphakic keratoplasty	261	10	3.8
Without vitreous manipulation	59	0	0
With vitreous manipulation	202	10	5.0
Combined procedure (penetrating keratoplasty and cataract extraction)	131	4	3.1
Without vitreous manipulation	72	0	0
With vitreous manipulation	59	4	6.8
Total aphakic and combined procedures	392	14	3.6
Without vitreous manipulation	131	0	0
With vitreous manipulation	261	14	5.4

keratoplasty (prior aphakia or cataract extraction at surgery) was 3.6%. Retinal detachments did not occur after those aphakic keratoplasties or combined procedures without vitreous manipulation, although an incidence of 2% could be expected. Since detachments were only found after those procedures involving vitreous manipulation, the 5.4% incidence of detachment that followed keratoplasty with vitrectomy (planned surgical vitreous loss) is significant.

This calculation, however, placed in proper perspective, may be a slight underestimation since some patients were lost to follow-up after graft failure and, prior to the advent of A-scan and B-scan ultrasonography here, there was no way to diagnose retinal detachment in a patient with an opaque graft. Since its introduction, ultrasonography is used both for preoperative retinal evaluation in patients with opaque corneas and for postoperative retinal evaluation in patients with opaque grafts. However, an important factor making the incidence of retinal detachment artificially high is that many aphakic patients underwent previous vitreous manipulation or loss and some had multiple vitreous disturbances leading to the development of corneal pathologic findings requiring keratoplasty. Pathologic findings in the vitreous cavity requiring vitrectomy included bands, cyclitic membrane, and even hemorrhagic membranes requiring removal for optic purposes. There is a greater incidence of detachment since one patient had a previous detachment and successful repair prior to the development of corneal pathologic findings.

The results of the surgery (Table 2) for retinal detachment after penetrating keratoplasty emphasize the poor prognosis. Of the two retinal detachments diagnosed elsewhere, one was inoperable and the other a surgical failure. Of the 12 detachments we diagnosed, six patients had total detachments and either declined surgery or their condition was inoperable. Two attempted repairs were unsuccessful at the time of surgery. One retina was initially attached but later detached behind an opaque graft, as shown by B-scan. Of three patients undergoing successful reattachments, two required two procedures. Final visual acuity in these two patients was counting fingers. The retina of one patient was reattached with one procedure and retained a clear graft, achieving visual acuity of 20/40.

The poor prognosis for detachment repair associated with keratoplasty may be related to inadequate visualization of the retina through the corneal transplant at the time of surgery, and to the difficulty in making an early diagnosis. This difficulty correlates well

TABLE 2

RESULTS OF RETINAL DETACHMENT SURGERY AFTER PENETRATING KERATOPLASTY

Case No., History	Graft*	Vitrectomy	Detachment	Results
1, Aphakic bullous keratopathy R.E. after bilateral cataract extraction, July 1970; previous diagnosis of Fuchs' dystrophy	PKP, Oct. 5, 1971, R.E.	Aspiration, cellulose sponge	Diagnosis Feb. 9, 1972: 270° detachment	Scleral buckle, Feb. 11; scleral resection, Feb. 15; successfully attached, subsequent graft failure
2, Aphakic bullous keratopathy R.E. after cataract extraction 1954; retinal detachment R.E. 1957, with successful repair	PKP, March 18, 1969, R.E.	Aspiration, cellulose sponge	Diagnosis, July 9: 180° detachment	Unsuccessful repair attempt, July 11
3, Aphakic bullous keratopathy L.E. after cataract extraction 1969	PKP, Feb. 8, 1971, L.E.	Aspiration, cellulose sponge	Diagnosis, May 5: total detachment	Declined surgery
4, Aphakic bullous keratopathy R.E. after cataract extraction 1967	PKP, Nov. 18, 1969, R.E.	Aspiration, cellulose sponge	Diagnosis, Dec. 29: total detachment	No repair attempted
5, Aphakic bullous keratoathy L. E. after cataract extraction 1969	PKP, Aug. 19, 1969, L.E.	Cellulose sponge	Diagnosis, Dec. 13: total detachment, early massive vitreous retraction	Declined surgery
6, Aphakic bullous keratopathy L.E. after cataract extraction 1970	PKP, Sept. 12, 1972, L.E.	Vitreous suction cutter	Diagnosis, April 11, 1973	Unsuccessful surgery, April 20
7, Failed lamellar graft for corneal ulcer 1965, R.E.; PKP and cataract extraction R.E. 1967, with subsequent graft failure	PKP, May 20, 1970, R.E.	Cellulose sponge	Diagnosis, June 7, 1973, at time of repeat PKP	Scleral buckle, July 17; scleral resection, July 25; successfully attached, clear graft
8, Aphakic bullous keratopathy R.E. after cataract extraction Jan. 1970	PKP, June 16, 1970, R.E. failed; PKP, Sept. 1, R.E.	Aspiration, cellulose sponge; aspiration, cellulose sponge	Diagnosis made elsewhere	No surgery attempted
9, Aphakic bullous keratopathy R.E. after cataract extraction April 1972	PKP, Aug. 1, 1972, R.E. failed; PKP, Dec. 3, R.E.	Vitreous suction cutter; vitreous suction cutter, cellulose sponge	Diagnosis, Jan. 3, 1973; total detachment with giant tear	No surgery attempted
10, Aphakic bullous keratopathy R.E. after cataract extraction June 1970	PKP, Aug. 13, 1971, L.E.	Aspiration, cellulose sponge	Diagnosis made elsewhere	Unsuccessful repair elsewhere
11, Fuchs' dystrophy with bullous keratopathy and cataract, L.E.	ICCE and PKP, Oct. 16, 1969, L.E.	Aspiration, cellulose sponge	Diagnosis; 180° detachment	Scleral buckle successfully attached, April 6, 1970; graft clear, visual acuity of 20/40
12, Interstitial keratitis and cataract, both eyes	ICCE and PKP, Jan. 2, 1973, R.E.	Vitreous suction cutter, cellulose sponge	Diagnosis, March 14; B-scan showed detachment	No repair attempted
13, Congenital cataract and corneal scar due to ulcer, R.E.	ICCE and PKP, Oct. 3, 1972, R.E.; PKP, Dec. 20, R.E.	Cellulose sponge; cellulose sponge	Detachment suspected, Nov. 14, 1972; detachment suspected at surgery, Dec. 20; definite detachment with giant tear, Dec. 27	Scleral resection, Dec. 28; successful attachment, subsequent graft failure; B-scan showed redetachment, Dec. 14, 1973
14, Corneal scar due to lye burn, R.E.	PKP and excision of lens remnant, Dec. 14, 1971, R.E.; repeat PKP, Dec. 14, 1972, R.E.	Aspiration	Diagnosis, Dec. 14, 1972: total detachment noted at time of repeat PKP for failed graft	No repair attempted

* PKP indicates penetrating keratoplasty; ICCE, intracapsular cataract extraction.

with the high incidence of totally detached retinas at the time of diagnosis (six of 12 patients). Late diagnosis also relates to the fact that only four patients had subjective complaints; eight patients were asymptomatic (Table 3). Poor visual acuity prior to, and immediately after, keratoplasty probably contributed to their ignorance of the problem.

Since only four (33%) patients had subjective complaints, ophthalmologists must be suspicious to make an early diagnosis. One clue is a qualitative decrease in visual acuity even though the visual acuity level may be low (for example, hand motions vs. counting fingers). Careful records should be kept regarding visual acuity. In patients whose fundus cannot be seen, any qualitative

change in the red reflex should be noted. A third indication may be an unexplained decrease in intraocular pressure (noted in three of 12 patients). Despite the difficulty with visualization, routine ophthalmoscopic examination should always be attempted; we diagnosed four detachments (33%) in this manner. Lastly, if a retinal detachment is suspected and the fundus cannot be seen, ultrasonography should be employed.

With regard to retinal detachment after penetrating keratoplasty, vitrectomy by aspiration of vitreous fluid in conjunction with cellulose sponges appears to be more traumatic to the retina than vitrectomy using the vitreous suction cutter. A new vitreophage[5-7] developed for anterior segment surgery may simplify vitrectomy while reducing its trauma. In addition, the vitreophage technique minimizes the use of cellulose sponges and this may reduce inflammation due to cellulose debris from these sponges. However, we do not have sufficient experience to determine whether the vitreophage will alter the incidence of retinal detachment. We do not conclude that vitrectomy is contraindicated. Vitrectomy has so clearly improved the prognosis of keratoplasty that it is often essential, although complications arise.

TABLE 3

FACTORS LEADING TO THE DIAGNOSIS OF RETINAL DETACHMENT AFTER PENETRATING KERATOPLASTY (12 PATIENTS)

	No. of Patients
Subjective complaints	
Decreased visual acuity	2
Visual field defect noted	1
Lightning flashes	1
Objective evidence	
Poor or absent red reflex	2
Made on routine ophthalmoscopic examination	4
Made at surgery	2

SUMMARY

Of 610 penetrating keratoplasties reviewed, retinal detachments did not occur after any phakic graft, or after aphakic or combined (keratoplasty and cataract extraction) procedures unless these were associated with vitreous manipulation. A 5.4% incidence of retinal detachment occurred after keratoplasty that involved vitrectomy. The resultant detachments had a poor prognosis probably because of delayed diagnosis and difficulties in visualization. Vitreous manipulation, therefore, may be essential to graft clarity but it is hazardous.

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RETROLENTAL FIBROPLASIA IN A FULL-TERM INFANT

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Terry[1] reported the first cases of retrolental fibroplasia (RLF) and erroneously attributed the findings to hyperplasia of a developmental remnant of the eye (tunica vasculosa lentis). Campbell[2] implicated oxygen as a causative agent in 1951. Since that time RLF generally has been considered as a disease of premature infants who received a high concentration of oxygen for a prolonged period of time.[3,4] Recently, however, we reviewed the record of a full-term infant who developed RLF after only brief exposure to supplemental oxygen.

CASE REPORT

A 3,800-g girl was born to a 26-year-old white woman Dec. 1, 1965, after 40 weeks' gestation. The expected due date was Nov. 26, 1965. Physical examination of the mother revealed a congenital Bell's palsy and absence of the right ear. The mother was O-positive, and results of serologic study were normal. During the pregnancy the mother received pyridoxine, thiamine, methylprednisolone acetate, and pyridoxine hydrochloride (Bendectin), on several occasions for hyperemesis gravidarum. There was a family history of diabetes mellitus but no record of glycosuria during the pregnancy.

The first stage of labor lasted 13 hours. The second stage lasted two hours and was terminated by oxytocin and elective low forceps at 10:44 A.M. The Apgar scores were 6 at one minute and 10 at five minutes. While awaiting transfer from the delivery room to the newborn nursery, the infant was described as dusky and crying poorly. For this reason the infant's oropharynx was aspirated and she was given intermittent positive pressure with 100% oxygen by mask and bag.

On admission to the newborn nursery at 11:10 A.M., she was placed in an incubator without supplemental oxygen. Physical examination at this time revealed normal full-term measurements: head circumference of 34.3 cm, chest circumference, 35.6 cm, and length, 40.8 cm. Her weight at 40 weeks' gestation (3,800 g) placed her in the "appropriate for gestational age" category.[5] Admission footprints revealed creases throughout the soles.

Her color remained pink until she was 24 hours of age, when she was noted to be slightly dusky, and a chest x-ray film was obtained. At 10:30 A.M., she was sent to the x-ray room. During the procedure a second episode of cyanosis occurred and the infant received 100% oxygen by mask. She returned by 12:00 A.M. Because the x-ray film revealed possible right upper lobe pneumonia, the baby was treated with penicillin and streptomycin. No further oxygen therapy was administered. Blood gases were not obtained. At 48 hours of age she was placed in an open crib. All medications were discontinued by 6 days of age and the patient was discharged two days later.

At 26 days of age, because of a possible tumor of the left eye, the patient had an ophthalmic examination with indirect ophthalmoscopy that established the diagnosis of RLF.

In the fundus of the right eye, there was evidence of traction on the retina. This was manifest as a slightly elevated fold running from the optic nerve head through the macula and into the temporal periphery where it expanded into a sheet of gray tissue. A massive vitreous hemorrhage was present at the far temporal periphery.

There was a highly elevated retinal fold in the fundus of the left eye. It extended from the optic disk through the macula into the temporal periphery and onto the pars plana from 2 o'clock to 4 o'clock, and behind the lens. There were several hemorrhages in the vitreous fluid over the peripheral temporal retina.

At age 6½ years, visual acuity was RE: 20/100, with a correction of $+1.50 = -3.50 \times 90°$, and L.E.: finger counting at 9 cm, unimproved on refraction. There was a left esotropia and hypertropia as well as searching nystagmus that was most pronounced in lateral gaze. The corneas were clear and of normal size. There was no evidence of cataract. Both fundi contained dense fibrous bands extending from the temporal periphery to the posterior pole.

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Discussion

Among the many questions pertaining to the pathogenesis of RLF there are at least two that cannot be definitively answered. The first is whether there is a causal relationship between the oxygen administered after birth and the RLF generally noticed some time thereafter. The second question is what constitutes a precipitating amount of oxygen.

This report documents the occurrence of RLF in a full-term infant with only minimal exposure to oxygen. Although the possibility of RLF occurring in a full-term infant has been alluded to for many years[5,6] few cases have been documented.[7,8] This infant was full term by birth weight and date and her head-to-chest proportion as well as her length and her sole creases were those of a full-term newborn. The eyes of a full-term infant may be susceptible to the development of RLF[9] because retinal vascularization at the temporal periphery is incomplete at 40 weeks' gestation.[10] Immature developing retinal vessels respond to increased tissue oxygenation by vasoconstriction, which is the first stage of RLF.[11,12] Even the retina that is fully vascularized will respond to increased tissue oxygenation by vasoconstriction.[12,13]

At first it would seem that this infant received no significant oxygen therapy, since the total possible duration of oxygen exposure was less than two hours. However, an elevated arterial oxygen tension may have occurred during either of the two episodes of oxygen administration. Although pulmonary vascular pressure is elevated during the first days of life,[14] when a newborn breathes 100% oxygen, the arterial oxygen tension may rise above 250 mm Hg.[15-17]

Cyanosis, as noted twice in this infant, might have been due to any of several common problems in the newborn such as hypoglycemia,[18] hypocalcemia,[19] or hypothermia.[20] When confronted with a cyanotic newborn one cannot wait until pulmonary pathologic findings are ruled out before giving oxygen that may be a life-saving procedure. As a result, when oxygen-enriched air is administered to a child with any of these conditions, the arterial oxygen tension will rise sharply since the pulmonary exchange of gases is unhindered.

Ophthalmologists should be aware that RLF can develop in the full-term infant. Oxygen must be monitored carefully when administered to any newborn and the possibility of RLF cannot be ignored merely because the infant is not premature.

Summary

A 3,800-g infant, born after 40 weeks' gestation, developed retrolental fibroplasia, documented by indirect ophthalmoscopy. Elevated arterial oxygen tensions may have occurred during brief treatment for two episodes of cyanosis.

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1906-1974

Book reviewing is a serious matter. It places a great responsibility on the editor and the reviewers, both with regard to the author and with regard to the readership. The editor must select a qualified reviewer. The reviewer whom he selects should be competent in the field with which the book deals in order to be able to evaluate it. But he must also approach it with an open mind. The reviewer should not be too personally involved, as occurs when he has a competitive book on the same subject. He should not be so egocentric as to use the book review solely as a vehicle to contrast his own wisdom with the limited ability of the author, or to give vent to his pet theories. Basically, a good book reviewer should love books. All this does not imply that a review should avoid criticism. As has been said, uncritical reviews are useless to the readership. Critical evaluations of methods, findings and conclusions are essential. But the criticism should be reasoned and constructive.

On the reviewing of books
Am. J. Ophthalmol. 66:756, 1968

KERATOPLASTY WOUND SEPARATIONS

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Recent publications have begun to explore the complications of, or the factors associated with, wound separations occurring after penetrating keratoplasty.[1,2] We analyzed 40 corneal transplant patients who developed wound separations at various times in their postoperative course.

MATERIALS AND METHODS

We examined the hospital records of keratoplasty patients with wound separations who had been examined by at least one of us after the wound separation, and reviewed the slit-lamp and Donaldson stereoscopic photographs of each patient, taken before and after the wound separation. Follow-up examination occurred between three months and three years after keratoplasty; the average follow-up was one year.

We removed interrupted sutures when deep blood vessels crossed the wound, when the sutures became loose, or when a visible wound scar was present. When using fine interrupted running sutures, we normally left the sutures in place for as long as possible. However, in children and in patients who had severely vascularized recipient tissue, we were sometimes forced to remove sutures as early as three or four weeks postoperatively due to exuberant vascularization and early graft rejection. Since this is a referral center, there may have been more of these complicated cases than would occur at random.

Alternate interrupted sutures were usually removed first.[3] Remaining interrupted sutures were removed one to two weeks later. The eight interrupted 10-0 monofilament nylon sutures that were used with the running 15-0 (13 μ) monofilament nylon sutures were removed for the same indications as for the interrupted 10-0 monofilament nylon sutures. Running sutures were removed for the same indications or when at least four or more months had elapsed.

All patients had intraocular pressures less than 30 mm Hg (MacKay-Marg) before suture removal. After administration of topical antibiotics and topical anesthesia, razor blade knives and jewelers forceps were used to remove sutures. Most sutures were removed at the slit lamp after insertion of a wire eyelid speculum. The remainder were removed under an operating microscope. A soft patch and metal eye shield were applied until examination the next morning.

In repairing separated wounds, limiting sutures were first placed at either end of a wound separation to prevent further separation during repair. These limiting sutures were placed by fixing at the corneoscleral limbus and pushing the needle through the intact wound at either end of the separation but not grasping the wound edge that might have caused further wound separation. We closed the remainder of the wound with multiple interrupted sutures and wound edge fixation was used as needed. Subconjunctival gentamicin sulfate (Garamycin) was given at the end of each procedure and the patients were then managed as new postkeratoplasty outpatients. Our corneal transplant techniques were described elsewhere.[4]

RESULTS

Incidence of wound separation—From Jan. 1, 1971, through April 30, 1973, the 369 penetrating keratoplasties we performed were consecutive and unselected except for the

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TABLE 1

PREOPERATIVE DIAGNOSIS OF PATIENTS WITH CORNEAL WOUND SEPARATIONS AFTER PENETRATING KERATOPLASTY

Diagnosis	No. of Cases	Previously Failed Corneal Transplants
Aphakic bullous keratopathy	17	—
Phakic bullous keratopathy	7	2
Interstitial keratitis	4	2
Keratoconus	3	1
Keratoconjunctivitis sicca	3	1
Alkali burn	1	0
Keratitis (etiology unknown)	1	1
Anterior chamber cleavage syndrome	1	—
Lattice corneal dystrophy	1	—
Congenital hereditary endothelial dystrophy	1	—
Traumatic leukoma	1	0
Total	40	7

many vascularized and complicated referral cases. During this period, 21 patients had a noticeable degree of wound gape, override, or separation, an incidence of 5.7%. In addition, we included four patients with wound separations prior to 1971, and 15 patients with wound separations who had corneal grafts after May 1, 1973, totaling 40 cases. These additional 19 cases were included to increase the number of cases for analysis but do not represent a consecutive unselected group.

Diagnosis—Phakic and aphakic bullous keratopathy and interstitial keratitis accounted for 28 of the cases (Table 1). The age range of the 20 females and 20 males was 2 to 92 years.

Original operative procedure—Twenty-two patients had had anterior vitrectomies by means of our vitreophage,[4] 12 had concurrent cataract extractions, and 13 received subtenon's injections of corticosteroids or soluble corticosteroids immediately after surgery. Interrupted 10-0 monofilament nylon sutures were used in 156 of the 369 corneal transplants (42%), running 10-0 monofilament nylon was used in 87 patients (24%), and running 15-0 (13 μ) monofilament nylon with eight interrupted 10-0 nylon sutures was used in 30 patients (8%). There appeared to be no significant difference in the incidence of wound separation when comparing the suture material in 21 patients who subsequently developed corneal wound separations with the suture material used in the 369 patients who had corneal transplants during the same period (Table 2). Although larger suture material appeared to be associated with a lower incidence of wound separation, this incidence was not statistically significant.

Twenty-six transplants were 7.5 mm and ten were 8.0 mm in diameter. The remainder were 6.0 mm, 7.0 mm, and 9.0 mm in diameter. Postoperatively, all but one patient received some form of topically applied 0.1% dexamethasone, at least four times daily. This patient received topically applied 0.1% dexamethasone, two times daily, the third through the eighth postoperative week only and developed a wound separation in the 13th postoperative week.

Development of wound separation relating to surgery—Most cases occurred within 12 weeks of the operation, but one, caused by trauma, occurred one year after the opera-

TABLE 2

COMPARISON OF SUTURE MATERIAL USED IN PENETRATING KERATOPLASTIES AND IN WOUND SEPARATIONS AFTER KERATOPLASTY

Suture	369 Keratoplasties No. of cases (%)	21 Wound Separations No. of cases (%)
10-0 interrupted	156 (42)	11 (47.6)
10-0 running	87 (24)	5 (28.6)
15-0 running	30 (8)	4* (19)
9-0 virgin silk, 9-0 nylon, 8-0 black silk	96 (26)	1 (4.8)

* Two of the four cases had the 15-0 suture inadvertently cut at the time of removal of the interrupted 10-0 suture used in conjunction with the running 15-0 suture.

tion (Table 3). We had other patients (not described here) whose wounds separated atraumatically when sutures were removed one year after corneal transplant.

Relationship between the timing of suture removal and development of wound separation—Wound separations that occurred immediately after the operation were due to technical problems encountered at surgery such as thin necrotic recipient beds. Six patients with wound separations before suture removal had severe secondary glaucoma with intraocular pressures greater than 40 mm Hg. Of the remaining patients who subsequently developed wound separations, 15 had intraocular pressures between 20 and 40 mm Hg, and ten had pressures greater than 40 mm Hg immediately after the operation; all pressures were controlled by the time of suture removal. Seventeen patients had evidence of wound separation within one day of suture removal (Table 4). Three wounds actually separated at the time of suture removal.

There were 29 cases in which a wound separation occurred after suture removal (Table 5). Six instances occurred when the running 15-0 suture was broken inadvertently at the time the accompanying interrupted 10-0 suture was removed. Most interrupted sutures were removed between six and ten weeks postoperatively, and most running sutures were removed after four months. In four cases, the running suture with its buried knot was removed early due to an unexpected overgrowth of vessels into the transplant that caused early typical graft rejection and was unresponsive to intense topical and subconjunctival therapy.

TABLE 3

CORNEAL WOUND SEPARATION AFTER PENETRATING KERATOPLASTY

Date, wks	No. of Cases
Immediately	5
1.5–4	11
5–12	15
13–20	3
21–28	5
49	1

TABLE 4

DEVELOPMENT OF CORNEAL WOUND SEPARATION IN RELATION TO DAY OF SUTURE REMOVAL

Date of Separation	No. of Cases
Immediately after keratoplasty	5
Before suture removal	6
Within one day of suture removal	17
Within two days of suture removal	4
1–4 wks after suture removal	6
14 wks	1
20 wks	1
Total	40

Location and type of wound separation—The location was predominantly distributed to the inferior and temporal quadrants. Twenty-one of the wound separations solely involved the anterior portion of the wound leaving the anterior chamber intact, while 19 developed full-thickness wound separations and flat anterior chambers (Table 6). Patients complained of sudden pain, severe photophobia, or a sudden gush of fluid over their eyelids.

TABLE 5

DATE OF SUTURE REMOVAL AFTER PENETRATING KERATOPLASTY

Date, wks	No. of Cases*	
	Interrupted Suture	Running Suture
3	2 (1)	0
4–6	11 (3)	0
7–8	3 (1)	1
9–10	2 (1)	0
11–13	1	3
17	0	1
21	1	1
25–28	0	2
44	0	1
Total	20	9

* Parentheses indicate interrupted sutures that were removed in conjunction with the 15-0 running suture.

TABLE 6

LOCATION OF CORNEAL WOUND SEPARATION AFTER PENETRATING KERATOPLASTY

Location	No. of Cases
Nasal	8
Inferior	12
Superior	5
Temporal	12
Multiple quadrants	3
Total	40

Sutures—Large silk sutures were used to repair wound separations in 22 cases and 10-0 monofilament nylon was used in ten cases. The full-thickness wound separations were easier to oppose than the anterior wound separations. Larger silk sutures were used more frequently in anterior wound separations because of the high tensile strength required to close the wound. These large sutures eventually pulled through the anterior stroma but kept the whole wound intact.

Although corneal vascularity was not precisely quantitated, vessels increased postoperatively (Table 7) despite corticosteroid injection at surgery and the frequent use of topically applied 0.1% dexamethasone postoperatively.

Visual acuity—Visual acuity was usually reduced after wound separation if there was a full-thickness separation (Table 8). Sixteen grafts remained clear and most of these had an anterior wound separation. Eighteen grafts were ultimately cloudy and three were borderline failures. Three grafts failed for varied reasons before wound separation.

Ten of 39 patient grafts were regrafted after wound separation, seven immediately, and three after late graft failure. Before retransplantation all ten patients had visual acuity of finger counting or light perception. One patient was lost to follow-up. Two of the remaining nine patients had no improvement in visual acuity after retransplantation and three were improved (20/200 to 20/400 range). Four showed improved visual acuity better than 20/100. Of 20 patients with postoperative visual acuity recorded before wound separation, six suffered a permanent loss of vision after wound separation (Table 9).

Graft reactions with concomitant iritis and immediate graft failure were common. More grafts failed immediately if a full thickness wound separation occurred. No evidence of stromal outgrowth occurred in this series.[5] Other complications included: late transplant failure, severe astigmatism, glaucoma, hyphema with vitreous hemorrhage (one case), endophthalmitis (two cases), and retinal detachment (one case).

DISCUSSION

The decision as to when to remove cornea sutures is usually based on the presence of adequate wound healing as evidenced by a contraction of the wound with loosening of sutures, ingrowth of deep stromal blood vessels, wound overgrowth of exuberant vascularization, early graft rejection episodes associated with vessel ingrowth, and the appearance of a white translucent scar in the wound. Simple corneal wounds appear to be histologically healed by the 45th postoperative day[6] and wounds closer to the corneoscleral limbus heal faster than more central wounds.[7] The lack of epithelium covering a corneal wound decreases the tensile strength of the wound.[7] Even with this knowledge and extreme care in removing corneal sutures we

TABLE 7

CORNEAL VASCULATURE* PREOPERATIVELY AND AT WOUND SEPARATION

	No. of Cases	
	Preoperative	Wound Separation
No vessels	23	15
Mild	10	17
Moderate	3	4
Severe	4	4

* No distinction could be made between deep and superficial vessels in this retrospective study.

are still faced with the problem of wound separations because there are not definite criteria for judging adequacy of wound healing.

Because of the appreciable amounts of wound separations, all corneal surgeons should be prepared to handle the resulting complications. The fact that 25 of the 39 patients with wound separations had corneal edema preoperatively in the recipient bed supports the theory that edematous corneas heal poorly.[1]

The evaluation of the effect of corneal wound vascularization on wound strength was difficult because we were unable to determine if the vessels described in the patients' records were deep or superficial. However, there appears to be an eventual increase in the amount of vascularization after keratoplasty (Table 6). In most of the cases there were few or no vessels in the wound separation areas, yet we had been forced to remove sutures in a distant area of the wound due to a dense focal ingrowth of vessels.

Subtenon's injections of corticosteroids at surgery in 13 cases and topical corticosteroids postoperatively in 30 patients did not reduce vascularization, but may have decreased wound healing. However, 27 patients did not receive subtenon's injections of corticosteroids at surgery and one patient received only topical corticosteroids, two times daily, for five weeks, and had no corticosteroids for five weeks before developing a wound separation.

TABLE 8

PREOPERATIVE AND POSTWOUND SEPARATION VISUAL ACUITY

Visual Acuity	No. of Cases	
	Preoperative	Wound Separation*
Hand motion to counting fingers	28	24
20/200–20/400	9	6
Better than 20/100	3	10

* Includes the best visual acuity of the ten patients with wound separations that were subsequently retransplanted.

TABLE 9

BEST VISUAL ACUITY POSTOPERATIVELY* (BEFORE WOUND SEPARATION) AND AFTER WOUND SEPARATION†

Case No.	Visual Acuity	
	After Keratoplasty	After Wound Separation and Repair
1	20/40	NLP
2	CF	CF
3	20/200	CF
4	CF	CF
5	CF	CF
6	20/40	CF
7	20/200	20/100
8	20/200	20/100
9	20/40	20/40
10	CF	CF
11	CF	20/400
12	20/100	20/25
13	CF	CF
14	20/80	20/80
15	20/400	20/200
16	20/200	CF
17	20/200	20/60
18	20/200	LP
19	20/200	CF
20	20/200	20/60

* Performed with a +12 lens and multiple pinhole disk.

† Six separations decreased, seven improved, and seven were unchanged.

The inferior and temporal location of the wound separations (Table 5) may indicate that strong orbicularis contraction may cause a wound separation.[8] Once a graft separates, or develops a wound override, the eyelids constantly traumatize the elevated edge and increase the amount of separation. Except for the six wound separations prior to suture removal, increased intraocular pressures did not appear to play a role in wound separation. Unlike other series, transplant size was not a factor.[9]

In repairing wound separations we carefully placed the first sutures into an area of intact corneal wound adjacent to the area of separation to prevent an "unzippering" of

the wound if sutures were placed directly in the area of separation first. Large silk sutures were used because more tension is required to pull a gaping anterior wound separation together. The limiting suture at the ends of the wound was placed in the intact wound without fixation at the edge.

These repair sutures are treated as if they are primary sutures and are removed when the clinical signs dictate. There were no occurrences of a reseparation after removal of repair sutures. This tends to support animal evidence that suturing of a previously opened corneal wound stimulates a more rapid and stronger healing.[7] Soft contact lenses were used in a few cases in an attempt to avoid repair, but eventually these wound separations were repaired.[10]

When a full-thickness corneal wound separation occurs, the prognosis for the transplant worsens. There is some evidence[11] that the mechanism of failure in these full-thickness separations may be due to a total separation of Descemet's membrane at the wound site.

Of the 19 patients with complete wound separations and flat anterior chambers, 12 had immediate graft failure and seven of these 12 required immediate retransplantation. The 21 patient grafts with anterior wound gapes were easier to repair and clinically had clearer transplants, yet there was more severe astigmatism and graft reaction in this group. Although leaving sutures in situ longer contributes additional tensile strength in avascular corneal wounds, there is no evidence that this is true beyond a limited time which has not been defined. It is unknown whether a wound at 12 months is stronger than at ten months or whether maximal strength may actually be achieved by three or four months. If graft clarity is judged as a basis of successful repair of a wound separation, then approximately 50% became cloudy and failed after a wound separation.

Recovery of visual acuity in patients with wound separations is possible (Tables 7 and 8). If a patient had poor postoperative visual acuity before wound separation, and later suffered a wound dehiscence, then the likelihood of recovering good visual acuity after the wound separation was also poor (Table 8). If visual acuity is good after keratoplasty and prior to wound separation, recovering good vision after wound repair is probable (Table 8). Of the ten patients who were immediately regrafted when their transplants dislodged after wound separation, 40% recovered good visual acuity and 30% had visual acuity between 20/200 and 20/400.

Twenty-one of 40 patients suffered wound separations within two days of suture removal (Table 4); 15 of the 21 separations occurred less than 12 weeks after keratoplasty (Table 3). Nine of the 15 had interrupted 10-0 monofilament nylon sutures (60%), three had running 10-0 sutures, and three had running 15-0 sutures that were inadvertently cut at the time of removal of the eight interrupted 10-0 sutures.

Our experience suggests that it is not the type of suture that is used nor the suture technique (running vs. interrupted) that predisposes to wound separation when 10-0 and 15-0 sutures are compared. If these sutures had remained longer the incidence of wound disruption might have been less, but sometimes the corneal surgeon is forced to remove sutures because the vascularization that was stimulated by the sutures does not cease. In addition, the presence of blood vessels may be associated with a graft rejection and the only way to stop the rejection process effectively is to remove the sutures. Some surgeons have implied that clean, buried fine sutures never stimulate vascularization but this is clearly incorrect, based on our experience, although the tendency to vascularize is reduced. If focal vascularization occurs in a graft with a running suture the surgeon must decide whether to risk the graft from vascular ingrowth in one area or wound separation in another. In patients with focal areas of recipient vascularization, we now use inter-

rupted sutures with buried knots since we have not found that removing sections of a running suture gives adequate support for the rest of the wound.

Those wound separations that occurred immediately after the operation were due to a variety of host factors such as necrotic or thin recipient tissue as well as technical problems encountered at surgery. The separations that occurred before suture removal were due to trauma.[12] In a group of patients who developed wound separations months after suture removal without any trauma, poor wound healing plus some unknown factor must be involved. In one case not included in this study, a 10-0 running suture was removed from a one-eyed woman (who had not received corticosteroids) one year after keratoplasty and the graft fell out, exhibiting virtually no healing.

Although precise data are not available in partial thickness separations when the graft remains thin and clear immediately after an anterior wound gape or partial override, Descemet's membrane and the endothelium, although stretched, may still be intact. This indicates a much better prognosis than a similar degree of apparent separation in which the graft thickens near the separation and the posterior layers may not have remained intact.

Summary

Forty cases of partial or full-thickness corneal wound separations after penetrating keratoplasty comprised three groups. One group of separations occurred before suture removal, due to technical problems encountered at surgery or increased intraocular pressure, or both. Most separations occurred immediately after suture removal and may be the most preventable. The third group of separations occurred long after suture-removal and may not be associated with obvious trauma.

About 50% of all wound separations caused graft failure, but patients with full-thickness wound separations had a worse prognosis for visual acuity recovery. Of those grafts that failed after wound separation and were retransplanted, there is a good chance of visual recovery. In our series, full-thickness wound separations or partial wound gape occurred in about 5.7% of our transplant cases. With delay of suture removal associated with a more adequate clinical means of evaluating wound healing, this number may be decreased.

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COMPLICATIONS OF MOHS' CHEMOSURGICAL EXCISION OF EYELID AND CANTHAL TUMORS

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There are few articles regarding complications of Mohs' chemosurgical excision of basal cell epitheliomas of the eyelids and canthal areas. An offshoot of this method, which has been called the "fresh" excisional technique, eliminates some of the problems of the chemical fixative but often does not spare the patient the necessity of secondary reconstructive surgery. These methods have excellent results; however, little attention has been focused on the complications and problems of such forms of therapy.

The chemosurgical technique for excision of skin tumors is based on in vivo fixation of tissue by zinc chloride paste.[1-3] The fixed tissue, from 0.05 to 0.20 cm thick, is pared from the unfixed underlying tissue and examined microscopically. The specimen is divided into multiple sections and marked with various stains to enable exact localization of areas positive for tumor. The process is repeated in stages until all areas positive for tumor are excised. The fresh technique usually involves staged excision without any prefixation.[3,4] With either technique, once the site is determined to be tumor free, it generally is permitted to heal by granulation. Proponents of such methods stress high rates of cure, safety to the patient, preservation of normal tissue and important structures, excellent cosmetic and functional results, and applicability to previously treated or inoperable lesions.[1-4] These claims must be weighed against the potential difficulties when the methods are used to treat cancer of the periorbital skin.

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We observed seven patients with basal cell epitheliomas of the canthi, eyelids, and periorbital skin and treated them after they had received prior treatment with either Mohs' chemosurgical or the fresh excisional techniques (Table).

CASE REPORTS

Case 1—A 69-year-old man with a basal cell epithelioma of the right medial canthal area was treated with radiation in 1966; a subsequent recurrence in this area (Fig. 1) was treated by Mohs' technique in four stages from Nov. 15 to 18, 1971. He was referred after sections from the deep medial canthus and eyelid margins were persistently positive for tumor.

After the final slough of tissue secondary to the chemical fixative, surgery was performed on Nov. 24, 1971. We noted an orbital ethmoid sinus fistula. There was persistent tumor in the lacrimal fossa, upper and lower eyelids, and over the medial rectus muscle (Fig. 2). The excision was completed and confirmed microscopically by free margins noted on frozen section. The resulting defect included exposed bone at the lacrimal fossa, the fistula behind the posterior lacrimal crest, and the medial one third of both eyelids (Fig. 3). A tarsoconjunctival flap was constructed from the remainder of the upper eyelid and positioned medially to reconstruct the missing medial part of both the upper and the lower eyelid. This flap was covered with a full-thickness postauricular skin graft. The orbital fistula persisted postoperatively; on March 30, 1972, a median forehead flap was used to cover the defect (Fig. 4). On Sept. 28, we performed an ethmoidectomy. To date, the fistula persists; the patient is tumor free and is reasonably satisfied with the surgical result. He is not interested in further reconstructive surgery for cosmetic purposes.

Case 2—An 81-year-old man had fresh excision of a basal cell epithelioma of his left cheek and lower eyelid. From Nov. 20 to 28, 1972, ten stages were required to eliminate the tumor. The defect extended deep to the bone from his left temple to the outer canthus, to nasal cartilage, and to the left side of his upper lip. It healed by granulation. By Dec. 21, he had severe conjunctival chemosis and exposure keratitis due to cicatricial ectropion of the left lower eyelid (Fig. 5). The patient refused corrective plastic surgery and died several months later from a myocardial infarction.

Case 3—A 70-year-old man presented with a 15-year history of basal cell epithelioma. His right

TABLE

COMPLICATIONS OF MOH'S CHEMOSURGICAL TREATMENT

Case No., Sex, Age (yrs)	Tumor Type	Earlier Treatment	Prior Excision Technique (No. of Stages)	Presenting Problems	Follow-up
1, M, 69	Basal cell	Radiation	Mohs (4)	Orbital sinus fistula positive sections at medial canthus	Symptom free, excellent results
2, M, 81	Basal cell		Fresh (10)	Cicatricial lagophthalmos, upper eyelid	Died, myocardial infarction
3, M, 70	Basal cell	Radiation, surgical	Mohs (8)	Cicatricial ectropion lower eyelid	Died, prostatic carcarcinoma
4, F, 57	Basal cell	Surgical	Fresh (4)	Positive sections at medial canthus	Symptom free, excellent results
5, F, 42	Basal cell	Surgical, radiation	Mohs (5)	Positive sections at medial canthus	Symptom free, excellent results
6, M, 75	Basal cell	Radiation	Mohs, 1 yr before (7)	Recurrent tumor at medial and lateral canthi and orbital extension	Tumor free, good functional results
7, F, 71	Basal cell	Radiation, surgical	Fresh (4)	Positive sections at medial canthus	Symptom free, excellent results

eye had been lost due to heavy radiation treatment for a lesion of the right lower eyelid. For 15 years, a recurrent tumor on the left of his forehead had been treated with four courses of radiation and at least three surgical excisions. From July 10 to 18, 1972, he had an eight-stage Mohs' excision that created a defect from the left postauricular area to the left upper eyelid, deep to periosteum in the supraorbital and temporal areas. The defect was allowed to heal by granulation (Fig. 6). On Jan. 9, 1973, the patient presented with a cicatricial lagophthalmos of the left upper eyelid. On Jan. 18, multiple adhesions were divided surgically and a full-thickness postauricular skin graft was used to cover the resulting defect (Fig. 7). The lagophthalmos was corrected by this operation. On this admission, the patient also had prostatic carcinoma and presumed bronchiogenic carcinoma. The patient died several months after the hospitalization.

Case 4—A 57-year-old woman had a 15-year history of basal cell epithelioma of the right medial canthal area, with two prior surgical excisions. From Feb. 26 to 28, 1973, she had a four-stage fresh excision that was abandoned because of residual tumor involvement of the eyelid margin and the proximity to the globe of positive tumor sections. On Feb. 28, complete surgical excision and repair were done. Positive tumor specimens were obtained from the right upper eyelid, lacrimal sac, ethmoid bone, and right cheek, before complete excision was confirmed by frozen sections. The resulting defect included the medial one third of both eyelids and defects over the right side of the nose and cheek. A tarsoconjunctival flap was developed from the upper eyelid and sutured medially to reconstruct the upper and lower eyelids. The flap

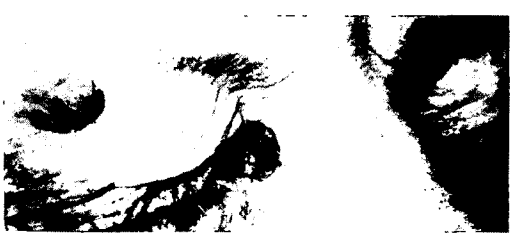


Fig. 1 (Baylis and Cies). Case 1. Right medial canthal basal cell epithelioma before Mohs' excision.



Fig. 2 (Baylis and Cies). Case 1. Right medial canthus after Mohs' excision, before surgical excision and plastic reconstruction.

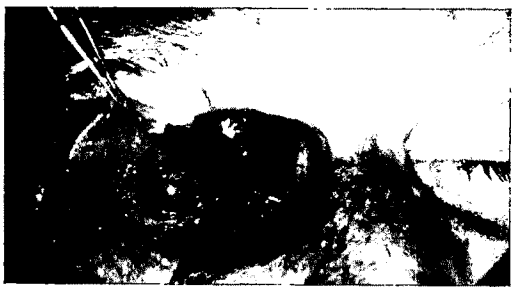


Fig. 3 (Baylis and Cies). Case 1. Resulting defect after complete excision of basal cell epithelioma, before plastic reconstruction.

and remaining skin defects were covered with full-thickness skin grafts (Fig. 8). She has had no recurrence to date, and the cosmetic result is excellent (Fig. 9).

Case 5—A 42-year-old woman with a six-year history of basal cell epithelioma of the right medial canthal area (as well as a history of several other basal cell epitheliomas of the face) had been treated previously by surgery and radiation therapy. From Jan. 29 to Feb. 2, 1973, a five-stage Mohs' chemosurgical excision was performed (Fig. 10), but the patient was referred because of residual positive section in the deep medial canthus and on both eyelid margins (Fig. 11). On Feb. 15, complete excision was performed, guided by frozen section examinations. The defect included the medial one third of the upper and lower eyelids and a large space about the medial canthus. A tarsoconjunctival flap from the upper eyelid was sutured medially to reconstruct the eyelids; a postauricular skin graft was used to cover the flap. Split-thickness skin grafts were used to cover the bare bone and cartilage of the nose (Fig. 12). Further surgery was performed on April 19, for cicatricial ectropion of the lower eyelid (Fig. 13). Subsequently, on June 14, a Jones tube conjunctivorhinostomy was performed because of complete loss of the lacrimal system. The patient has remained in good health to date and has achieved good cosmetic and functional results.

Case 6—A 75-year-old man had radiation treatment of a basal cell epithelioma of the right cheek



Fig. 4 (Baylis and Cies). Case 1. Two weeks after median forehead flap to repair persistent defect and fistula.



Fig. 5 (Baylis and Cies). Case 2. Three weeks after fresh excision of basal cell epithelioma of left cheek, showing cicatricial ectropin of left lower eyelid. Healing was by granulation.

in 1968, with resulting loss of the anterior aspect of his nose. After being followed for seven months for suspicious growths on his left cheek and lower eyelid, he had a seven-stage fresh excision of a basal cell epithelioma from Nov. 7 to 15, 1972. This lesion recurred a year later, and since it appeared to involve both the medial and lateral canthi and to be invading the orbit, the patient was referred for total surgical excision. On Dec. 20, 1973, surgery was performed. Excision was carried deep into the orbit along the orbital floor and into both canthi. A large rotation cheek flap was used to cover the defect, which included the entire lower eyelid and both canthi. The patient has been free of tumor with an adequate functional result.

Case 7—A 71-year-old woman with a 15-year history of basal cell epithelioma of the left medial canthal area had been treated previously with radiation and three surgical excisions. Beginning June 19, 1972, she had four stages of fresh excision, which was abandoned due to extensive deep involvement by the tumor (Fig. 14). On June 26, full excision was carried to the bone at the canthus, with a large superficial nasal defect and loss of the medial half of both eyelids (Fig. 15). A large upper eyelid tarsoconjunctival flap was sutured to the bone medially and covered with full-thickness skin grafts to recreate the medial aspects of both eyelids. Split-thickness skin grafts were used to cover the exposed bone and cartilage of the nose. On June 7, 1973, the tarsoconjunctival flap was opened to form a normal palpebral fissure. The

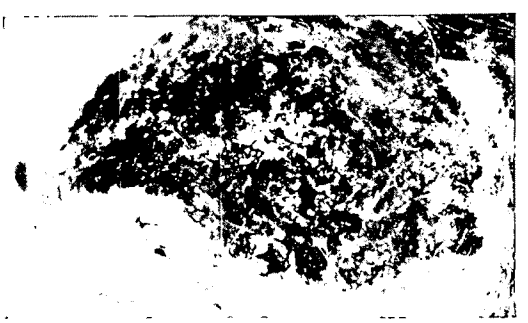


Fig. 6 (Baylis and Cies). Case 3. Early granulation one week after completion of Mohs' excision of basal cell epithelioma of the left forehead.



Fig. 7 (Baylis and Cies). Case 3. One week after the repair of cicatricial lagophthalmos of the left upper eyelid with full-thickness skin graft.



Fig. 9 (Baylis and Cies). Case 4. Ten weeks after complete excision and plastic reconstruction of a basal cell epithelioma of the right medial canthus.

patient has been asymptomatic with an excellent functional and cosmetic result (Fig. 16).

Discussion

Basal cell epitheliomas of the eyelids and canthi present a difficult problem in that good function and cosmesis are sought along with complete eradication of the tumor. Many patients have a long history of tumor involvement and often of multiple treatments. Six of our patients had a history of prior radiation or surgical excision, or both. Their history of tumor involvement ranged from four to 15 years. In all cases the tumors were advanced, and complete excision represented a formidable task. The Mohs' or the fresh techniques with their low rates of recurrence appeared particularly applicable to these seven patients.

Perhaps the basic reason for the excellent rate of cure in Mohs' technique is the system employed for marking specimens. Various stains, including merbromin (Mercurochrome), Prussian blue, and india ink, are used to mark the specimen in a coded pattern, carefully charted for reference. When pathologists read slides of this specimen, the particular stains enable them to localize exactly the areas positive for tumor. This localization enables the physician to direct exci-



Fig. 8 (Baylis and Cies). Case 4. Three days after complete excision of a basal cell epithelioma of the right medial canthus and plastic reconstruction.



Fig. 10 (Baylis and Cies). Case 5. After several sessions of Mohs' excision of a basal cell epithelioma of the right medial canthus.



Fig. 11 (Baylis and Cies). Case 5. At termination of Mohs' chemosurgery, with a sizeable defect and continued erosion of eyelid margins by chemicals.

sion to areas with residual tumor. This process often requires multiple sessions for several days until tumor eradication is complete.[1]

Zinc chloride is an excellent in vivo fixative, but its use on periorbital tissue must be judicious, for it is extremely caustic and it can penetrate deeply. The depth of penetration and fixation is controlled qualitatively by the thickness and duration of paste application. The fixative is said to kill superficial nerve fibers and render the process painless,[1] but, in fact, it can be uncomfortable to the patient.[5,6] The excision is directed along the plane between fixed and unfixed tissues. Four to ten days after the final fixation and



Fig. 12 (Baylis and Cies). Case 5. Five days after complete surgical excision and plastic reconstruction.



Fig. 13 (Baylis and Cies). Case 5. Ten weeks after complete surgical excision and plastic reconstruction of the right medial canthal lesion.

excision session, the last application of zinc chloride paste causes a final slough of tissue,[1-6] as in Case 1. Marked inflammatory changes in response to the chemical delayed definitive surgery six days (Case 1), and 12 days (Case 5). One patient (Case 5) had continued erosion of eyelid margins several days after termination of chemosurgery. In Case 1, the fixative may have eroded bone into the ethmoid sinus, causing the orbital sinus fistula. These difficulties seem to indicate that the criteria for abandoning chemosurgery are a greater extent of fixation than desired; continued erosion of eyelid margin or vital structures; or tumor proximity to the globe, where contact with the caustic paste may damage the cornea, muscles, conjunctiva, or sclera.

Mohs[4] has used the fresh technique for



Fig. 14 (Baylis and Cies). Case 7. At the termination of Mohs' chemosurgery for basal cell epitheliomas of the left medial canthus and right brow.

tumors of the eyelid margin since 1952. Basically, it is surgical excision without prior fixation. Basic to both methods are the staged multiple excisions that permit the systematic analysis of the excised tissue to direct the subsequent staged excisions. In our patients, this process required from four stages over four days (Case 1) to ten stages over nine days (Case 2). In two patients (Cases 1 and 5) (chemosurgery) and two more patients (Cases 4 and 7) (fresh excisional), the staged excisions were terminated when the specimens from deep medial canthal or vital ocular structures were persistently positive for tumor cells as the excisions progressed. The technical difficulties of controlling the fixative paste or of repeated excisions in a lamellar fashion in the cramped medial canthus, with its vital structures, militated against continuation of this process.

In both techniques, after excision is completed, healing is by granulation. This process can be lengthy and can result in scarring and distortion of the eyelids. In Case 2, three weeks after surgery, there was cicatricial ectropion of the lower eyelid with resulting severe conjunctival chemosis and exposure keratitis. In Case 3, after several months, severe cicatricial lagophthalmos of the left upper eyelid precluded complete closure of the eyelid. Robins, Henkind, and Menn[7] recently reported two cases of successful excision of basal cell epithelioma in the medial canthal area, that healed by granulation but required secondary reconstructive surgery for functional and cosmetic reasons. Thus, although Mohs[1-3] cites excellent functional results from this method of healing, these patients illustrate the potential problems of repair by granulation.



Fig. 15 (Baylis and Cies). Case 7. Several days after termination of Mohs' excision showing continued erosion of eyelid margins by chemicals.



Fig. 16 (Baylis and Cies). Case 7. Fourteen months after the surgical excision and plastic reconstruction.

Our method of treating patients who have had prior chemosurgery or staged fresh surgery is basically the same as that described in the seven cases. If there has been chemosurgery, surgery is delayed until the inflammation subsides and the final slough of fixed tissue occurs. Total excision of any residual tumor must be insured by microscopic confirmation of tumor-free margins around the lesion. In Case 5, 15 sections were obtained to confirm free margins before reconstruction was begun. In Cases 1, 4, 5, and 7, the large medial defect was repaired by constructing an upper eyelid tarsoconjunctival flap and suturing this flap medially to provide the tarsal backbone of the upper and lower eyelids as well as a functional medial canthal ligament.[8] A full-thickness skin graft from postauricular or upper eyelid skin is used to cover this flap and any defect over the nose or cheek areas. Secondary procedures are required occasionally for creating the medial palpebral fissure (Case 7), correcting cicatricial ectropion (Case 5), or relieving epiphora when the nasolacrimal duct is lost

(Case 5). In Case 3, we treated the cicatricial distortion of the eyelids by lysing all adhesions and covering the resulting skin defect with full-thickness skin grafts.

Our experience with these seven patients reveals some potential difficulties with Mohs' chemosurgery or the fresh surgical technique. Through direct contact or uncontrolled erosion, the fixative paste can present a threat to sensitive ocular structures. The fresh technique avoids the chemical problems. Both methods, however, are staged excisions and technically may be difficult to execute in the medial canthal area to excise a tumor completely without harming vital ocular structures. Secondary reconstructive surgery may be necessary to alleviate problems associated with healing by granulation, particularly if the lesion is quite large. Finally, this process of tumor excision represents a lengthy procedure of multiple surgical sessions followed by a protracted period of healing. Because there is a potential for such problems, any physician employing these techniques should have access to an ophthalmic surgeon who is familiar with eyelid and orbital reconstruction.

Summary

Seven patients with basal cell epithelioma of the eyelids, canthi, or periorbital skin who were initially treated by Mohs' chemosurgery or by fresh-staged excisions developed complications directly referable to the initial method of excision. Five patients achieved excellent results. Methods of one-stage complete excision and plastic reconstruction were used when tumor excision was incomplete. When excision was complete, secondary reconstructive surgery was sometimes necessary to assuage the effects of healing by granulation.

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IMMUNOGLOBULINS IN THE HUMAN CORNEA

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Stock and Aronson,[1] in a study of 13 eyes from nine persons, reported that immunoglobulins G (IgG) and A (IgA) were present in peripheral and central corneas but immunoglobulin M (IgM) was not. The relationship of corneal to serum levels, which might substantiate serum as the source of corneal immunoglobulins, was not a part of their study. In a report[2] designed to study immunoglobulins in various parts of the entire eye, we occasionally found IgM in the cornea and by simultaneously studying serum levels found some indication that corneal and serum immunoglobulin levels corresponded.

We restudied the observations of Stock and Aronson[1] on immunoglobulins in the cornea, and analyzed the relationships of immunoglobulins in the cornea to those in the serum.

SUBJECTS AND METHODS

Subjects—Eyes were removed at autopsy from ten randomly selected subjects whose personal characteristics are listed in Table 1. The four men and six women ranged in age from 29 to 75 years. Eyes were removed five to 26 hours post mortem along with a blood sample from the heart or a great vessel.

Processing of eyes—Within an hour or so of enucleation we removed the cornea from each globe by cutting at the corneoscleral limbus and excluding all sclera. A central button of cornea was then removed with a 5-mm trephine. This button became "piece 5" for each left eye (Fig. 1). We cut the remaining doughnut-shaped corneal rings into four equal quadrants and labeled them (Fig. 1).

Extraction of immunoglobulins from the corneal pieces—Phosphate-buffered saline at pH 7.4 was placed in 0.1-ml amounts into ten 10 × 74-mm disposable glass tubes for each set of eyes. Tubes were numbered, capped with a paraffin sealer, and weighed to an accuracy of 0.1 mg. One excised piece of cornea was placed in each tube and the tube (plus its buffer and cornea piece) was reweighed. The difference between the first and second weighing was the wet weight of the corneal tissue.

To allow a better exchange between buffer and corneal fluids, we partially macerated the cornea by jabbing it several times with a sharp probe. The tubes were incubated for 48 to 72 hours at 37°C to equilibriate the immunoglobulin inside the corneal piece with the buffer. No preservatives were used. Significant bacterial growth was noted in only one of the tubes. The eluates were transferred into small plastic self-capping centrifuge tubes in preparation for the analysis procedure.

Analysis of immunoglobulins—The eluting fluid was analyzed for IgG, IgA, IgM, and albumin content in a single radial immunodiffusion technique.[3] Lower limit for immunoglobulin detection was 5 mg/100 ml.

Immunoglobulin and albumin content of corneal pieces—The immunoglobulin and albumin content of the equilibrated fluids is expressed in milligrams per 100 milliliters (Table 2). The amount of immunoglobulin in each corneal piece was calculated by the following formula:

$$Ca = \frac{(W + V \cdot g)Cb}{W}$$

where Ca is the concentration of protein in the tissue in milligrams per 100 milliliters of

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TABLE 1

IDENTIFYING DATA ON DONORS OF EYES STUDIED

Case No., Age, Sex (yrs)	Cause of Death	Eyes Removed After Death, hrs
1, 60, Female	Metastatic endometrial cancer	20
2, 62, Female	Reticulum cell sarcoma	14
3, 69, Male	Cancer of the lung	7
4, 75, Male	Cancer of the stomach	12
5, 51, Male	Leukemia and erythroid hypoplasia	14
6, 48, Female	Squamous cell cancer of the pharynx, drug ingestion, coma, septicemia	26
7, 53, Male	Myocardial infarction	20
8, 72, Female	Bronchial pneumonia	12
9, 29, Male	Bronchogenic cancer	5
10, 59, Male	Aortic stenosis	9

tissue; *Cb* is the concentration of protein in the eluting fluid in milligrams per 100 milliliters; *W* is the weight of the tissue in grams; *g* is the specific gravity of the tissue in grams per milliliter; and *V* is the original volume of the eluting fluid in milliliters. For the purposes of calculation, the specific gravity of the cornea was 1 (actually it is 1.05).[4] It was also assumed that the amount of immunoglobin in a given corneal volume at equilibrium was the same as the amount in a corresponding volume of eluting fluid. We realize that this assumption is erroneous because, for example, cornea is known to be

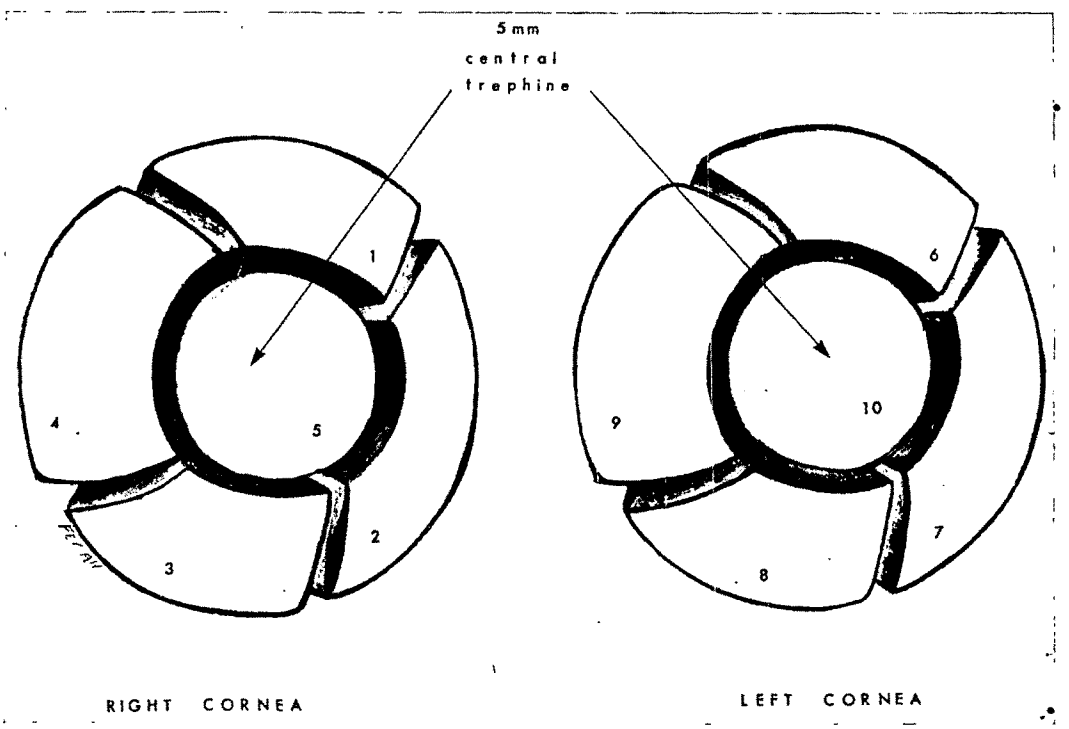


Fig. 1 (Allansmith and McClellan). Method of dividing cornea into peripheral and central portions. Each cornea was cut into five pieces.

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5, F, 42	Basal cell	Surgical, radiation	Mohs (5)	Positive sections at medial canthus	Symptom free, excellent results
6, M, 75	Basal cell	Radiation	Mohs, 1 yr before (7)	Recurrent tumor at medial and lateral canthi and orbital extension	Tumor free, good functional results
7, F, 71	Basal cell	Radiation, surgical	Fresh (4)	Positive sections at medial canthus	Symptom free, excellent results

eye had been lost due to heavy radiation treatment for a lesion of the right lower eyelid. For 15 years, a recurrent tumor on the left of his forehead had been treated with four courses of radiation and at least three surgical excisions. From July 10 to 18, 1972, he had an eight-stage Mohs' excision that created a defect from the left postauricular area to the left upper eyelid, deep to periosteum in the supraorbital and temporal areas. The defect was allowed to heal by granulation (Fig. 6). On Jan. 9, 1973, the patient presented with a cicatricial lagophthalmos of the left upper eyelid. On Jan. 18, multiple adhesions were divided surgically and a full-thickness postauricular skin graft was used to cover the resulting defect (Fig. 7). The lagophthalmos was corrected by this operation. On this admission, the patient also had prostatic carcinoma and presumed bronchiogenic carcinoma. The patient died several months after the hospitalization.

Case 4—A 57-year-old woman had a 15-year history of basal cell epithelioma of the right medial canthal area, with two prior surgical excisions. From Feb. 26 to 28, 1973, she had a four-stage fresh excision that was abandoned because of residual tumor involvement of the eyelid margins and the proximity to the globe of positive tumor sections. On Feb. 28, complete surgical excision and repair were done. Positive tumor specimens were obtained from the right upper eyelid, lacrimal sac, ethmoid bone, and right cheek, before complete excision was confirmed by frozen sections. The resulting defect included the medial one third of both eyelids and defects over the right side of the nose and cheek. A tarsoconjunctival flap was developed from the upper eyelid and sutured medially to reconstruct the upper and lower eyelids. The flap



Fig. 1 (Baylis and Cies). Case 1. Right medial canthal basal cell epithelioma before Mohs' excision.



Fig. 2 (Baylis and Cies). Case 1. Right medial canthus after Mohs' excision, before surgical excision and plastic reconstruction.



Fig. 3 (Baylis and Cies). Case 1. Resulting defect after complete excision of basal cell epithelioma, before plastic reconstruction.

and remaining skin defects were covered with full-thickness skin grafts (Fig. 8). She has had no recurrence to date, and the cosmetic result is excellent (Fig. 9).

Case 5—A 42-year-old woman with a six-year history of basal cell epithelioma of the right medial canthal area (as well as a history of several other basal cell epitheliomas of the face) had been treated previously by surgery and radiation therapy. From Jan. 29 to Feb. 2, 1973, a five-stage Mohs' chemosurgical excision was performed (Fig. 10), but the patient was referred because of residual positive section in the deep medial canthus and on both eyelid margins (Fig. 11). On Feb. 15, complete excision was performed, guided by frozen section examinations. The defect included the medial one third of the upper and lower eyelids and a large space about the medial canthus. A tarsoconjunctival flap from the upper eyelid was sutured medially to reconstruct the eyelids; a postauricular skin graft was used to cover the flap. Split-thickness skin grafts were used to cover the bare bone and cartilage of the nose (Fig. 12). Further surgery was performed on April 19, for cicatricial ectropion of the lower eyelid (Fig. 13). Subsequently, on June 14, a Jones tube conjunctivorhinostomy was performed because of complete loss of the lacrimal system. The patient has remained in good health to date and has achieved good cosmetic and functional results.

Case 6—A 75-year-old man had radiation treatment of a basal cell epithelioma of the right cheek



Fig. 4 (Baylis and Cies). Case 1. Two weeks after median forehead flap to repair persistent defect and fistula.



Fig. 5 (Baylis and Cies). Case 2. Three weeks after fresh excision of basal cell epithelioma of left cheek, showing cicatricial ectropin of left lower eyelid. Healing was by granulation.

in 1968, with resulting loss of the anterior aspect of his nose. After being followed for seven months for suspicious growths on his left cheek and lower eyelid, he had a seven-stage fresh excision of a basal cell epithelioma from Nov. 7 to 15, 1972. This lesion recurred a year later, and since it appeared to involve both the medial and lateral canthi and to be invading the orbit, the patient was referred for total surgical excision. On Dec. 20, 1973, surgery was performed. Excision was carried deep into the orbit along the orbital floor and into both canthi. A large rotation cheek flap was used to cover the defect, which included the entire lower eyelid and both canthi. The patient has been free of tumor with an adequate functional result.

Case 7—A 71-year-old woman with a 15-year history of basal cell epithelioma of the left medial canthal area had been treated previously with radiation and three surgical excisions. Beginning June 19, 1972, she had four stages of fresh excision, which was abandoned due to extensive deep involvement by the tumor (Fig. 14). On June 26, full excision was carried to the bone at the canthus, with a large superficial nasal defect and loss of the medial half of both eyelids (Fig. 15). A large upper eyelid tarsoconjunctival flap was sutured to the bone medially and covered with full-thickness skin grafts to recreate the medial aspects of both eyelids. Split-thickness skin grafts were used to cover the exposed bone and cartilage of the nose. On June 7, 1973, the tarsoconjunctival flap was opened to form a normal palpebral fissure. The

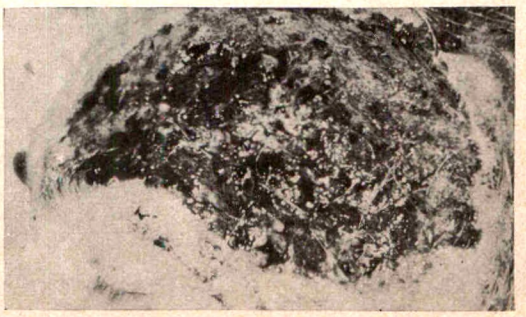


Fig. 6 (Baylis and Cies). Case 3. Early granulation one week after completion of Mohs' excision of basal cell epithelioma of the left forehead.

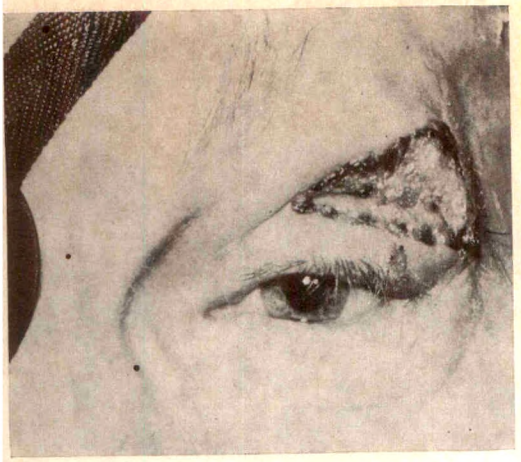


Fig. 7 (Baylis and Cies). Case 3. One week after the repair of cicatricial lagophthalmos of the left upper eyelid with full-thickness skin graft.

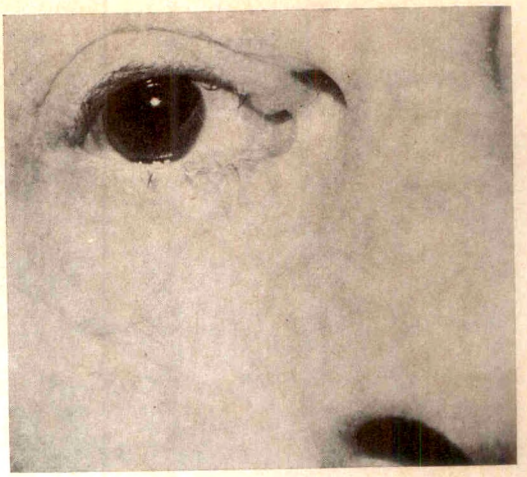


Fig. 9 (Baylis and Cies). Case 4. Ten weeks after complete excision and plastic reconstruction of a basal cell epithelioma of the right medial canthus.

patient has been asymptomatic with an excellent functional and cosmetic result (Fig. 16).

Discussion

Basal cell epitheliomas of the eyelids and canthi present a difficult problem in that good function and cosmesis are sought along with complete eradication of the tumor. Many patients have a long history of tumor involvement and often of multiple treatments. Six of our patients had a history of prior radiation or surgical excision, or both. Their history of tumor involvement ranged from four to 15 years. In all cases the tumors were advanced, and complete excision represented a formidable task. The Mohs' or the fresh techniques with their low rates of recurrence appeared particularly applicable to these seven patients.

Perhaps the basic reason for the excellent rate of cure in Mohs' technique is the system employed for marking specimens. Various stains, including merbromin (Mercurochrome), Prussian blue, and india ink, are used to mark the specimen in a coded pattern, carefully charted for reference. When pathologists read slides of this specimen, the particular stains enable them to localize exactly the areas positive for tumor. This localization enables the physician to direct exci-

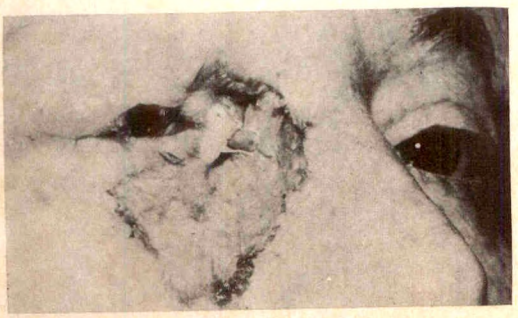


Fig. 8 (Baylis and Cies). Case 4. Three days after complete excision of a basal cell epithelioma of the right medial canthus and plastic reconstruction.



Fig. 10 (Baylis and Cies). Case 5. After several sessions of Mohs' excision of a basal cell epithelioma of the right medial canthus.

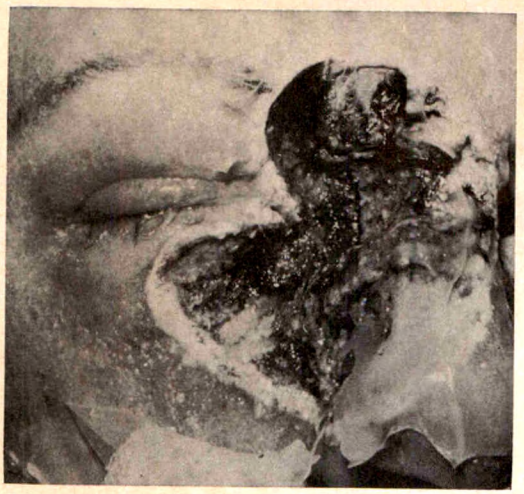


Fig. 11 (Baylis and Cies). Case 5. At termination of Mohs' chemosurgery, with a sizeable defect and continued erosion of eyelid margins by chemicals.

sion to areas with residual tumor. This process often requires multiple sessions for several days until tumor eradication is complete.[1]

Zinc chloride is an excellent in vivo fixative, but its use on periorbital tissue must be judicious, for it is extremely caustic and it can penetrate deeply. The depth of penetration and fixation is controlled qualitatively by the thickness and duration of paste application. The fixative is said to kill superficial nerve fibers and render the process painless,[1] but, in fact, it can be uncomfortable to the patient.[5,6] The excision is directed along the plane between fixed and unfixed tissues. Four to ten days after the final fixation and

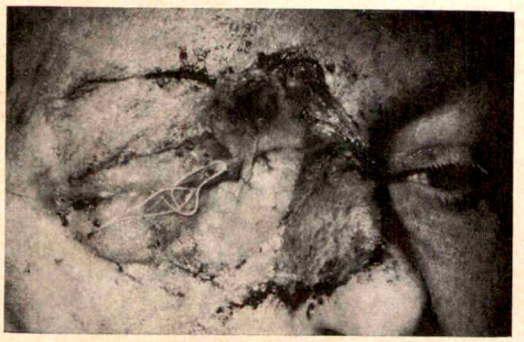


Fig. 12 (Baylis and Cies). Case 5. Five days after complete surgical excision and plastic reconstruction.

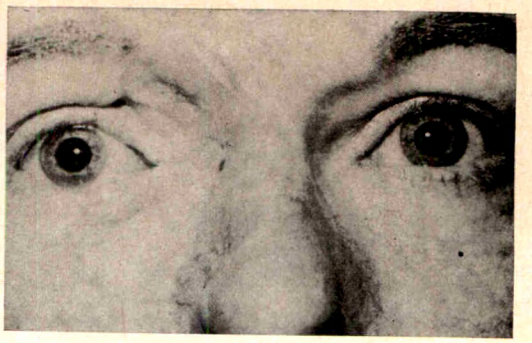


Fig. 13 (Baylis and Cies). Case 5. Ten weeks after complete surgical excision and plastic reconstruction of the right medial canthal lesion.

excision session, the last application of zinc chloride paste causes a final slough of tissue,[1-6] as in Case 1. Marked inflammatory changes in response to the chemical delayed definitive surgery six days (Case 1), and 12 days (Case 5). One patient (Case 5) had continued erosion of eyelid margins several days after termination of chemosurgery. In Case 1, the fixative may have eroded bone into the ethmoid sinus, causing the orbital sinus fistula. These difficulties seem to indicate that the criteria for abandoning chemosurgery are a greater extent of fixation than desired; continued erosion of eyelid margin or vital structures; or tumor proximity to the globe, where contact with the caustic paste may damage the cornea, muscles, conjunctiva, or sclera.

Mohs[4] has used the fresh technique for



Fig. 14 (Baylis and Cies). Case 7. At the termination of Mohs' chemosurgery for basal cell epitheliomas of the left medial canthus and right brow.

tumors of the eyelid margin since 1952. Basically, it is surgical excision without prior fixation. Basic to both methods are the staged multiple excisions that permit the systematic analysis of the excised tissue to direct the subsequent staged excisions. In our patients, this process required from four stages over four days (Case 1) to ten stages over nine days (Case 2). In two patients (Cases 1 and 5) (chemosurgery) and two more patients (Cases 4 and 7) (fresh excisional), the staged excisions were terminated when the specimens from deep medial canthal or vital ocular structures were persistently positive for tumor cells as the excisions progressed. The technical difficulties of controlling the fixative paste or of repeated excisions in a lamellar fashion in the cramped medial canthus, with its vital structures, militated against continuation of this process.

In both techniques, after excision is completed, healing is by granulation. This process can be lengthy and can result in scarring and distortion of the eyelids. In Case 2, three weeks after surgery, there was cicatricial ectropion of the lower eyelid with resulting severe conjunctival chemosis and exposure keratitis. In Case 3, after several months, severe cicatricial lagophthalmos of the left upper eyelid precluded complete closure of the eyelid. Robins, Henkind, and Menn[7] recently reported two cases of successful excision of basal cell epithelioma in the medial canthal area, that healed by granulation but required secondary reconstructive surgery for functional and cosmetic reasons. Thus, although Mohs[1-3] cites excellent functional results from this method of healing, these patients illustrate the potential problems of repair by granulation.



Fig. 15 (Baylis and Cies). Case 7. Several days after termination of Mohs' excision showing continued erosion of eyelid margins by chemicals.



Fig. 16 (Baylis and Cies). Case 7. Fourteen months after the surgical excision and plastic reconstruction.

Our method of treating patients who have had prior chemosurgery or staged fresh surgery is basically the same as that described in the seven cases. If there has been chemosurgery, surgery is delayed until the inflammation subsides and the final slough of fixed tissue occurs. Total excision of any residual tumor must be insured by microscopic confirmation of tumor-free margins around the lesion. In Case 5, 15 sections were obtained to confirm free margins before reconstruction was begun. In Cases 1, 4, 5, and 7, the large medial defect was repaired by constructing an upper eyelid tarsoconjunctival flap and suturing this flap medially to provide the tarsal backbone of the upper and lower eyelids as well as a functional medial canthal ligament.[8] A full-thickness skin graft from postauricular or upper eyelid skin is used to cover this flap and any defect over the nose or cheek areas. Secondary procedures are required occasionally for creating the medial palpebral fissure (Case 7), correcting cicatricial ectropion (Case 5), or relieving epiphora when the nasolacrimal duct is lost

(Case 5). In Case 3, we treated the cicatricial distortion of the eyelids by lysing all adhesions and covering the resulting skin defect with full-thickness skin grafts.

Our experience with these seven patients reveals some potential difficulties with Mohs' chemosurgery or the fresh surgical technique. Through direct contact or uncontrolled erosion, the fixative paste can present a threat to sensitive ocular structures. The fresh technique avoids the chemical problems. Both methods, however, are staged excisions and technically may be difficult to execute in the medial canthal area to excise a tumor completely without harming vital ocular structures. Secondary reconstructive surgery may be necessary to alleviate problems associated with healing by granulation, particularly if the lesion is quite large. Finally, this process of tumor excision represents a lengthy procedure of multiple surgical sessions followed by a protracted period of healing. Because there is a potential for such problems, any physician employing these techniques should have access to an ophthalmic surgeon who is familiar with eyelid and orbital reconstruction.

Summary

Seven patients with basal cell epithelioma of the eyelids, canthi, or periorbital skin who were initially treated by Mohs' chemosurgery or by fresh-staged excisions developed complications directly referable to the initial method of excision. Five patients achieved excellent results. Methods of one-stage complete excision and plastic reconstruction were used when tumor excision was incomplete. When excision was complete, secondary reconstructive surgery was sometimes necessary to assuage the effects of healing by granulation.

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IMMUNOGLOBULINS IN THE HUMAN CORNEA

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Stock and Aronson,[1] in a study of 13 eyes from nine persons, reported that immunoglobulins G (IgG) and A (IgA) were present in peripheral and central corneas but immunoglobulin M (IgM) was not. The relationship of corneal to serum levels, which might substantiate serum as the source of corneal immunoglobulins, was not a part of their study. In a report[2] designed to study immunoglobulins in various parts of the entire eye, we occasionally found IgM in the cornea and by simultaneously studying serum levels found some indication that corneal and serum immunoglobulin levels corresponded.

We restudied the observations of Stock and Aronson[1] on immunoglobulins in the cornea, and analyzed the relationships of immunoglobulins in the cornea to those in the serum.

SUBJECTS AND METHODS

Subjects—Eyes were removed at autopsy from ten randomly selected subjects whose personal characteristics are listed in Table 1. The four men and six women ranged in age from 29 to 75 years. Eyes were removed five to 26 hours post mortem along with a blood sample from the heart or a great vessel.

Processing of eyes—Within an hour or so of enucleation we removed the cornea from each globe by cutting at the corneoscleral limbus and excluding all sclera. A central button of cornea was then removed with a 5-mm trephine. This button became "piece 5" for each left eye (Fig. 1). We cut the remaining doughnut-shaped corneal rings into four equal quadrants and labeled them (Fig. 1).

Extraction of immunoglobulins from the corneal pieces—Phosphate-buffered saline at pH 7.4 was placed in 0.1-ml amounts into ten 10 × 74-mm disposable glass tubes for each set of eyes. Tubes were numbered, capped with a paraffin sealer, and weighed to an accuracy of 0.1 mg. One excised piece of cornea was placed in each tube and the tube (plus its buffer and cornea piece) was reweighed. The difference between the first and second weighing was the wet weight of the corneal tissue.

To allow a better exchange between buffer and corneal fluids, we partially macerated the cornea by jabbing it several times with a sharp probe. The tubes were incubated for 48 to 72 hours at 37°C to equilibriate the immunoglobulin inside the corneal piece with the buffer. No preservatives were used. Significant bacterial growth was noted in only one of the tubes. The eluates were transferred into small plastic self-capping centrifuge tubes in preparation for the analysis procedure.

Analysis of immunoglobulins—The eluting fluid was analyzed for IgG, IgA, IgM, and albumin content in a single radial immunodiffusion technique.[3] Lower limit for immunoglobulin detection was 5 mg/100 ml.

Immunoglobulin and albumin content of corneal pieces—The immunoglobulin and albumin content of the equilibrated fluids is expressed in milligrams per 100 milliliters (Table 2). The amount of immunoglobulin in each corneal piece was calculated by the following formula:

$$Ca = \frac{(W + V \cdot g)Cb}{W}$$

where Ca is the concentration of protein in the tissue in milligrams per 100 milliliters of

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TABLE 1

IDENTIFYING DATA ON DONORS OF EYES STUDIED

Case No., Age, Sex (yrs)	Cause of Death	Eyes Removed After Death, hrs
1, 60, Female	Metastatic endometrial cancer	20
2, 62, Female	Reticulum cell sarcoma	14
3, 69, Male	Cancer of the lung	7
4, 75, Male	Cancer of the stomach	12
5, 51, Male	Leukemia and erythroid hypoplasia	14
6, 48, Female	Squamous cell cancer of the pharynx, drug ingestion, coma, septicemia	26
7, 53, Male	Myocardial infarction	20
8, 72, Female	Bronchial pneumonia	12
9, 29, Male	Bronchogenic cancer	5
10, 59, Male	Aortic stenosis	9

tissue; *Cb* is the concentration of protein in the eluting fluid in milligrams per 100 milliliters; *W* is the weight of the tissue in grams; *g* is the specific gravity of the tissue in grams per milliliter; and *V* is the original volume of the eluting fluid in milliliters. For the purposes of calculation, the specific gravity of the cornea was 1 (actually it is 1.05).[4] It was also assumed that the amount of immunoglobin in a given corneal volume at equilibrium was the same as the amount in a corresponding volume of eluting fluid. We realize that this assumption is erroneous because, for example, cornea is known to be

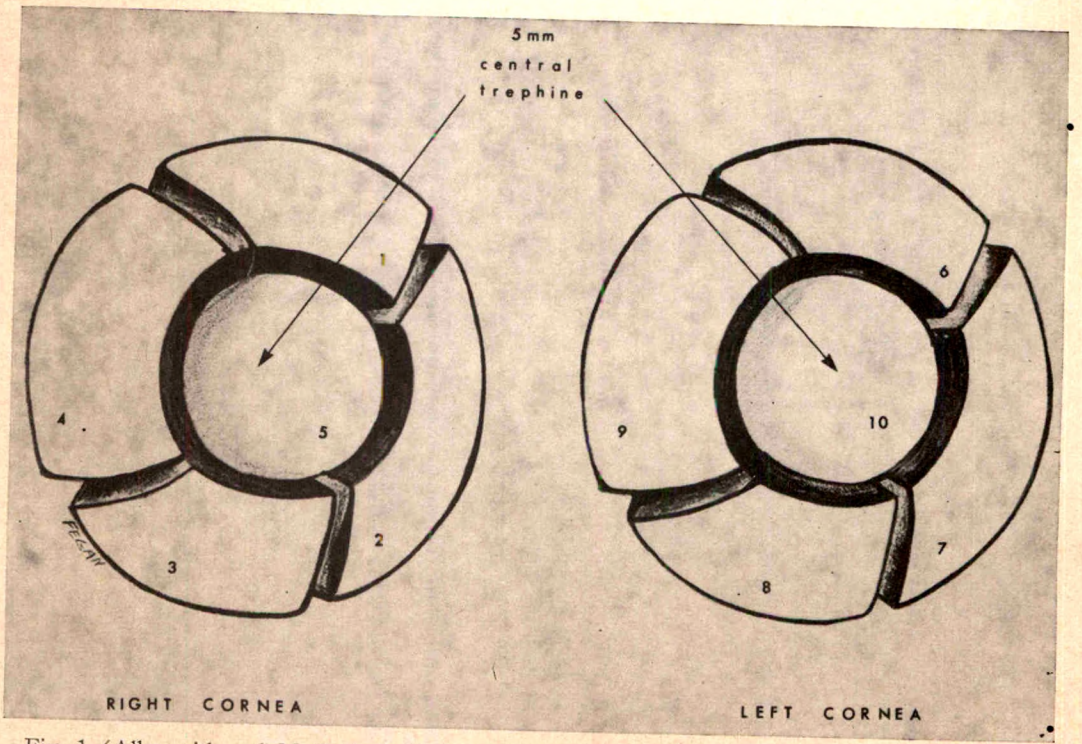


Fig. 1 (Allansmith and McClellan). Method of dividing cornea into peripheral and central portions. Each cornea was cut into five pieces.

TABLE 2

IMMUNOGLOBULIN AND ALBUMIN LEVELS* IN CORNEAS† AND SERA OF 10 SUBJECTS

	1	2‡	3	4	5	6	7	8	9	10	Average
IgG											
Cornea	625	259	310	856	645	107	455	568	410	648	463
Serum	978	466	1280	1820	640	257	1057	1089	1154	911	965
IgA											
Cornea	128	34	28	44	106	39	64	60	68	87	66
Serum	389	86	334	145	395	163	249	473	418	180	309
IgM	(2/10)	(10/10)	(1/10)	(9/10)	(2/10)	(9/10)	(10/10)	(10/10)	(10/10)	(10/10)	
Cornea	0	122	0	38	0	22	0	6	0	12	9
Serum	110	25	21	128	64	75	68	114	134	253	100
Albumin	(8/10)	(2/10)	—	(10/10)	(6/10)	(9/10)	—	—	—	—	
Cornea	769	724	—	114	378	163					256
Serum	2850	1670	2500	1600	1060	1350	—	—	—	—	1838

* Levels measured as milligrams per 100 milliliters; numbers in parentheses indicate the number of pieces tested/maximum number of pieces available per subject; dash indicates nontested.
† The number for each cornea represents the average for all pieces tested from both eyes.
‡ Values from Case 2 excluded (see text).

only 75% water and some of that is bound and unavailable as a solution.[5] The assumption was made for ease in calculation.

We determined serum immunoglobulin and albumin content by radial immunodiffusion in the same way as for the corneal extracts.

Recovery of human immunoglobulins injected into the rabbit cornea—Measured amounts of human sera were injected intralamellarly into the central corneal areas of three living rabbits (Table 3). The immunoglobulin content of the human sera (used for the three rabbits) was determined. The injected fluid was allowed to diffuse for 3½ hours for two rabbits and 24 hours for the third rabbit (Table 3). The animals were killed, eyes removed, and corneas processed as for human corneas.

Statistics—Correlation coefficients and Student's t-test were used,[6] and linear regression lines were calculated.

RESULTS

IgG—Immunoglobulin G was detected in all corneal pieces tested (Table 2), ranging from a low of 107 mg/100 ml to 856 mg/100 ml, with an average of 463 mg/100 ml. Thus, on a weight basis, the cornea contained about one half as much IgG as the serum (Table 2).

The peripheral and central cornea contained equal amounts of IgG (Figs. 2 and 3).

The amount of IgG in a right cornea matched the amount in the fellow left cornea ($r = .88$, $P < .001$) (Fig. 4). The level of IgG in the cornea also correlated with the level of IgG in the serum ($r = .76$, $P < .025$) (Fig. 5).

TABLE 3

RECOVERY OF SERUM IMMUNOGLOBULINS INJECTED INTO RABBIT CORNEAS

Rabbit No.	Diffusion Time, hrs	Cornea	Volume of Serum Injected	Mg Injected*			Mg Recovered			Percent Recovered		
				IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM
1	3½	Right	0.03 ml	0.4881	0.0876	0.0513	0.2149	0.0464	0.0337	44	53	66
		Left	0.045 ml	0.7322	0.1314	0.0769	0.3518	0.0774	0.0636	48	59	83
2	3½	Right	0.05 ml	0.8135	0.1460	0.0855	0.3258	0.0653	0.0409	40	45	48
		Left	Normal saline	0	0	0	0	0	0	0	0	0
3	24	Right	0.04 ml	0.6508	0.1168	0.0684	0.1246	0.0379	trace	19	32	0
		Left										

* Calculated from milligrams per 100 milliliters in serum and volume injected.
† Described in text.

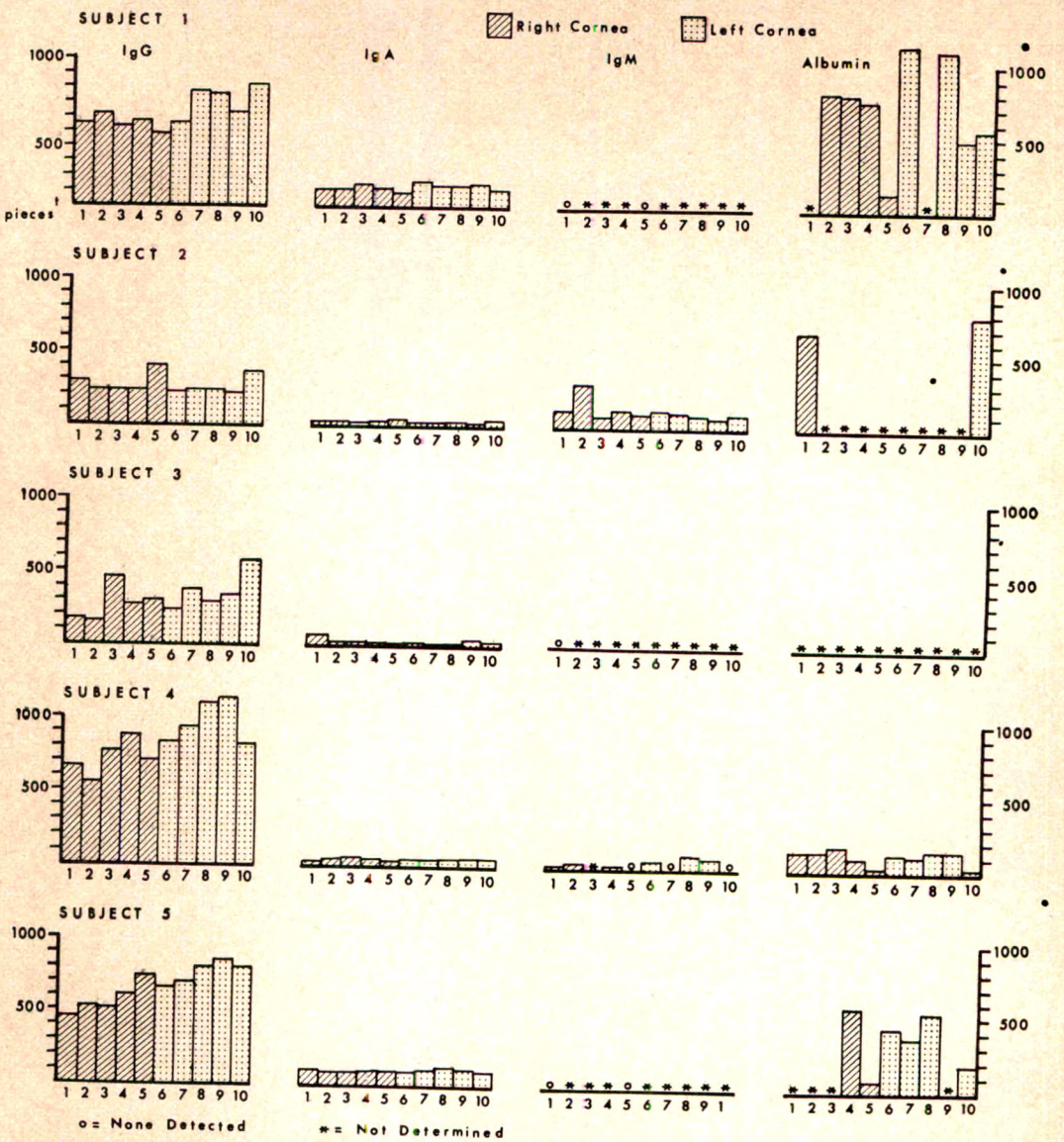


Fig. 2 (Allansmith and McClellan). Cases 1-5. Distribution of immunoglobulins and albumin (milligram per 100 milliliters) in various areas of the cornea.

IgA: Immunoglobulin A was detected in all but two of the 100 corneal pieces (Figs. 2 and 3). On the average, the cornea contained about one-fifth the concentration of IgA as the serum (Table 2). It was evenly distributed across the cornea as was IgG. The central and peripheral cornea contained about the same amount of IgA (Figs. 2 and 3). The amount of IgA in the right cornea matched the amount in the fellow left cornea ($r = .95$, $P < .001$) (Fig. 6). Corneal IgA, unlike corneal IgG, did not correlate with the serum level ($r = .56$, $P > .1$) (Fig. 7).

IgM—We tested for the presence of IgM in most corneal pieces in seven subjects (Cases 2, 4, 6, and 8-10). In the remaining three (Cases 1, 3, and 5), one or two

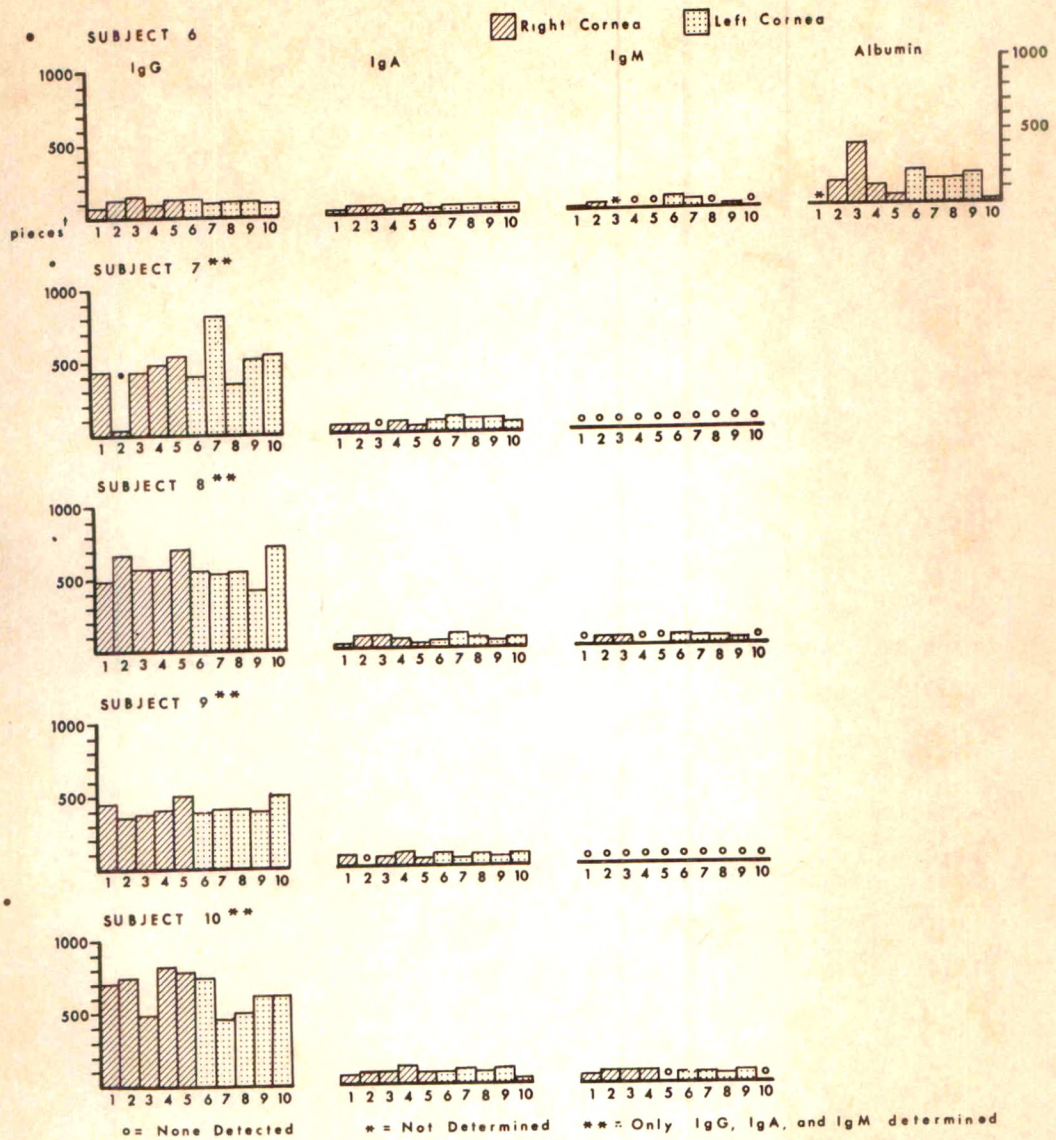


Fig. 3 (Allansmith and McClellan). Cases 6-10. Distribution of immunoglobulins and albumin (milligram per 100 milliliters) in various areas of the cornea.

corneal pieces of each subject were tested (Figs. 2 and 3). The concentration of IgM was higher in each of the ten corneal pieces than in one subject's serum (Case 2); this did not occur in any of the other nine subjects (Table 2). Also, the average IgG or IgA level was never higher in the cornea than in the serum. Because of the peculiarity of the elevated IgM in both corneas (Case 2), these data were excluded from IgM comparisons of the central and peripheral sections and in calculations for average IgM content of one cornea (Table 2).

Of 16 of 20 central corneal pieces tested for the presence of IgM, only one subject (Case 2) showed IgM. Comparison of IgM in peripheral and central cornea showed significantly less IgM in the central cornea ($P < .01$).

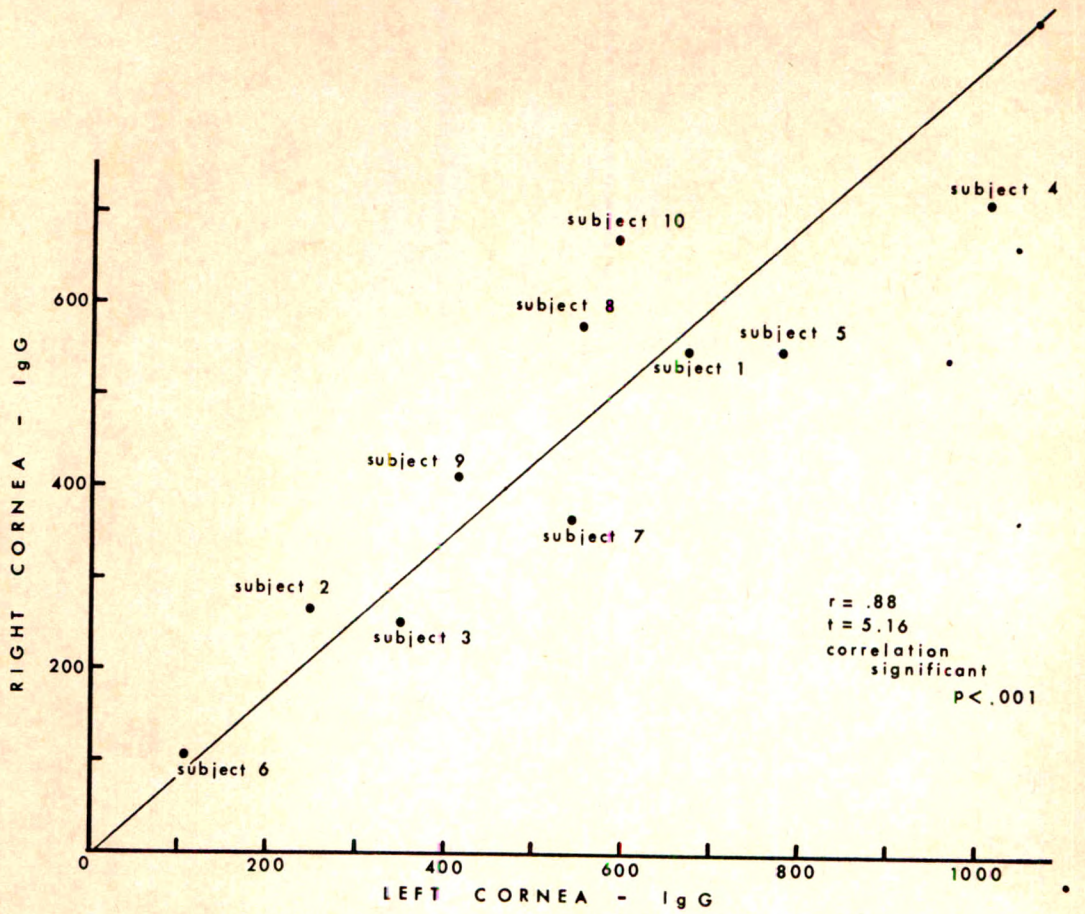


Fig. 4 (Allansmith and McClellan). Comparison of IgG (milligram per 100 milliliters) in corneas of ten subjects.

The amount of IgM in the cornea, approximately one-fourth when present, was the serum level. The corneal and serum levels were not correlated ($r = .246$, $P > .05$).

Albumin—Albumin was present in all corneal pieces tested (35 of 35). We tested most pieces in four subjects (Cases 1, and 4-6). The central buttons were significantly lower in albumin than in the peripheral corneal pieces ($P < .05$). The amount of albumin in the corneal was about one fifth that in the serum. The ratio of peripheral to central albumin in these subjects was 3:1. Corneal to serum concentrations of albumin were not analyzed because the number completed was too small.

To determine if the various immunoglobulins could be desorbed from the cornea at the same rate in a given time, serum was injected intralamellarly into the centers of rabbit corneas (Table 3). The immunoglobulin content of the injected serum was 1,627 mg/100 ml for IgG, 292 mg/100 ml for IgA, and 17 mg/100 ml for IgM. About one half of all three immunoglobulins was recovered after a 3½-hour diffusion period for two rabbits. One eye that was examined after a 24-hour diffusion period demonstrated less of all three immunoglobulins than at 3½ hours. The unusually low amount of IgM recovered is unexplained.

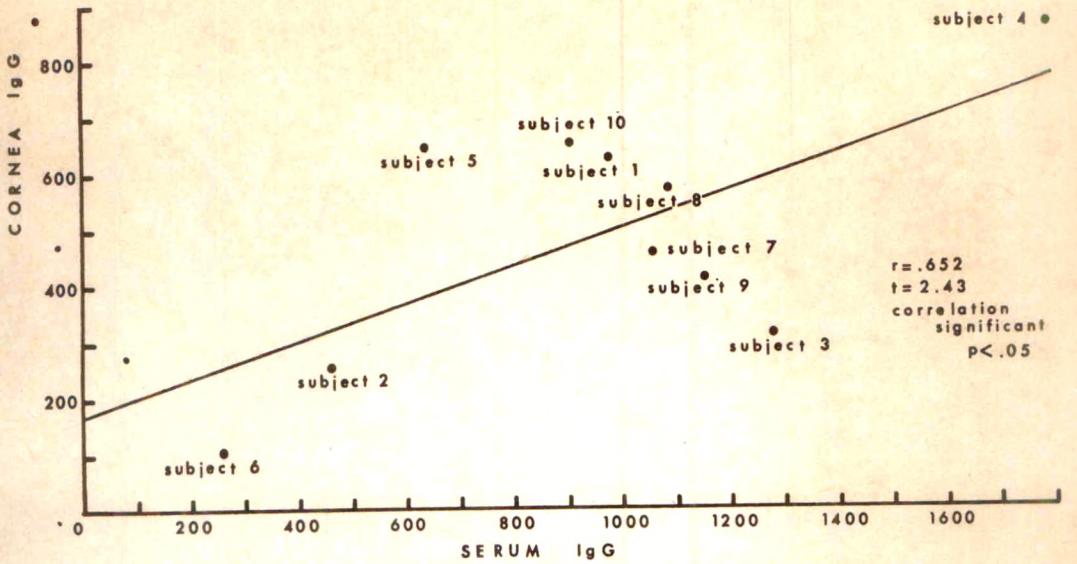


Fig. 5 (Allansmith and McClellan). Comparison of IgG (milligram per 100 milliliters) in corneas and sera of ten subjects.

Postmortem effect on immunoglobulin recovery—We examined the amount of immunoglobulin recovered from the human cornea and related to the number of hours post mortem. Time after death made no significant difference in the pattern of recovery for any immunoglobulin or albumin ($P > .1$ overall comparison).

Discussion

Immunoglobulins in the human cornea are probably derived from the serum. Their levels are so high when compared to tears[7] or aqueous humor[2] that no other source seems plausible. This opinion is strengthened by the significant correlation of corneal and serum IgG levels (Fig. 5). Holt and Kinoshita[8] found that over one half of soluble proteins of the bovine cornea were serum proteins. Maurice and Watson[9] assumed that the albumin they extracted from the rabbit cornea originated from blood. Krause[10] first noted that the cornea contained the blood proteins. Antibodies present in the blood probably will also be present in the corneal stroma.

The cornea has more IgG at higher concentrations than other ocular tissues studied.[2] Our average IgG content was about one half that of serum (Table 2). Stock and Aronson[1] found IgG was one tenth of the serum levels. The difference between the studies is unexplained especially since the amount of IgG found in conjunctivae and sera was about the same for both groups.[1,2] In contrast to the situation reported for albumin,[9] no apparent loss of IgG across the endothelium occurred. The central cornea contained the same amount of IgG as the peripheral cornea ($P > .10$).

Immunoglobulin A is one-fifth the serum level in the cornea. As with IgG, IgA is evenly distributed across the cornea. Stock and Aronson[1] found IgA was about $\frac{1}{20}$ the serum level in the cornea. Again, their levels of IgA in the conjunctiva were approximately the same as ours.

Immunoglobulin M sometimes enters the corneal periphery (Figs. 2 and 3), but the circumstances are unclear. Stock and Aronson[1] did not detect IgM or another macromolecule (β_1C, a component of complement) in 13 corneas.

Several paradoxic relationships between

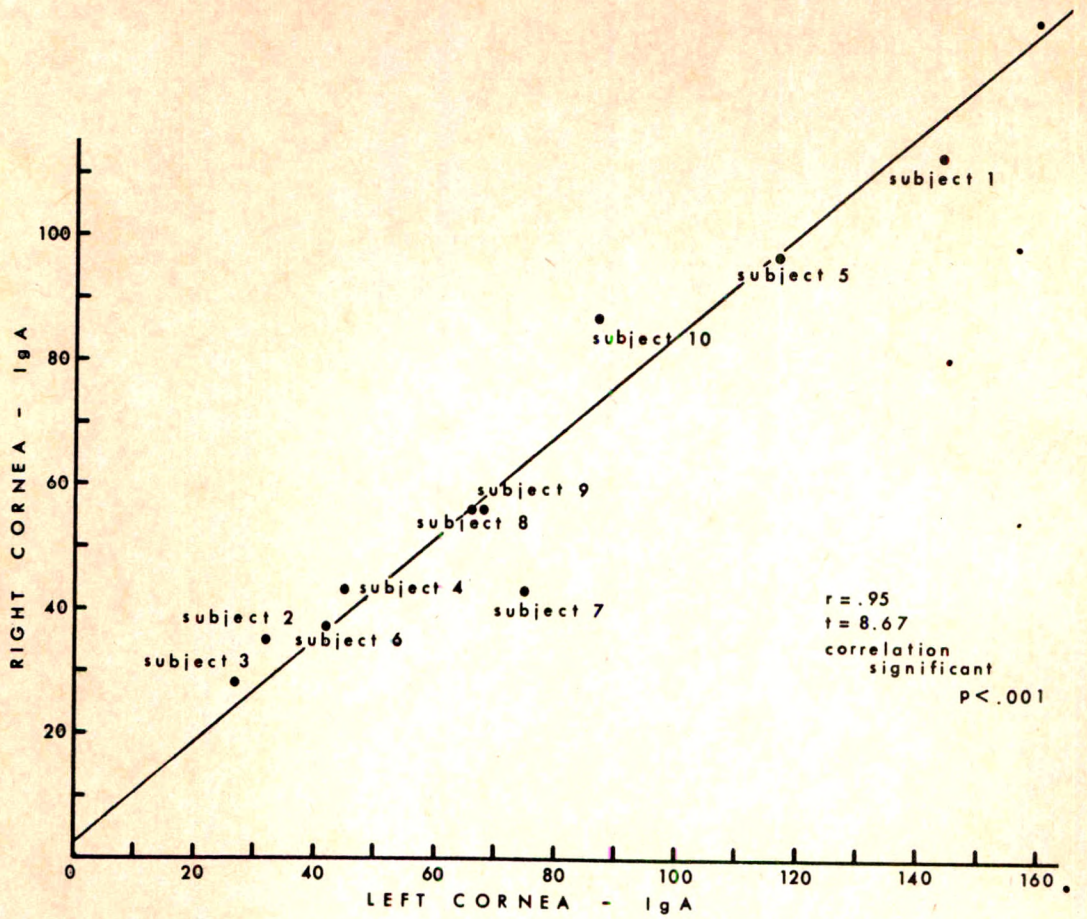


Fig. 6 (Allansmith and McClellan). Comparison of IgA (milligram per 100 milliliters) in corneas of ten subjects.

the corneal immunoglobulins occurred. First, the IgG-to-IgA ratio for serum, probably the source of corneal immunoglobulins, is significantly lower at 3:1 than the cornea at 7:1 (Table 2) ($P < .05$). The amount of IgG and IgA in one cornea of a set paradoxically correlates better with IgG and IgA in the fellow cornea than with amounts in the serum (Figs. 4 and 6).

We postulate that the cornea has a different exclusion volume for each type of macromolecule. With molecules larger than approximately 170,000 mol. wt., the ability of the corneal stroma to exclude differentially the molecules is more important than the effect of the serum concentration. To support this postulation, we showed that while serum IgG (150,000 mol. wt.)[11] correlates with corneal IgG (Figure 5, $P < .05$), serum IgA (170,000 mol. wt.)[11] does not correlate with corneal IgA ($P < .1$, Figure 7).

The exclusion volume for one type of macromolecule is a personal characteristic and is probably more important in determining corneal levels than availability of molecules from the serum. To support this, the correlation coefficient for either IgG or IgA in the right cornea compared with the fellow left cornea was $r = .88$, $P < .001$ for IgG, and $r = .95$, $P < .001$ for IgA, whereas the serum-to-corneal IgG correlation was $r = .76$, $P < .025$, and IgA in the serum to cornea did not significantly correlate

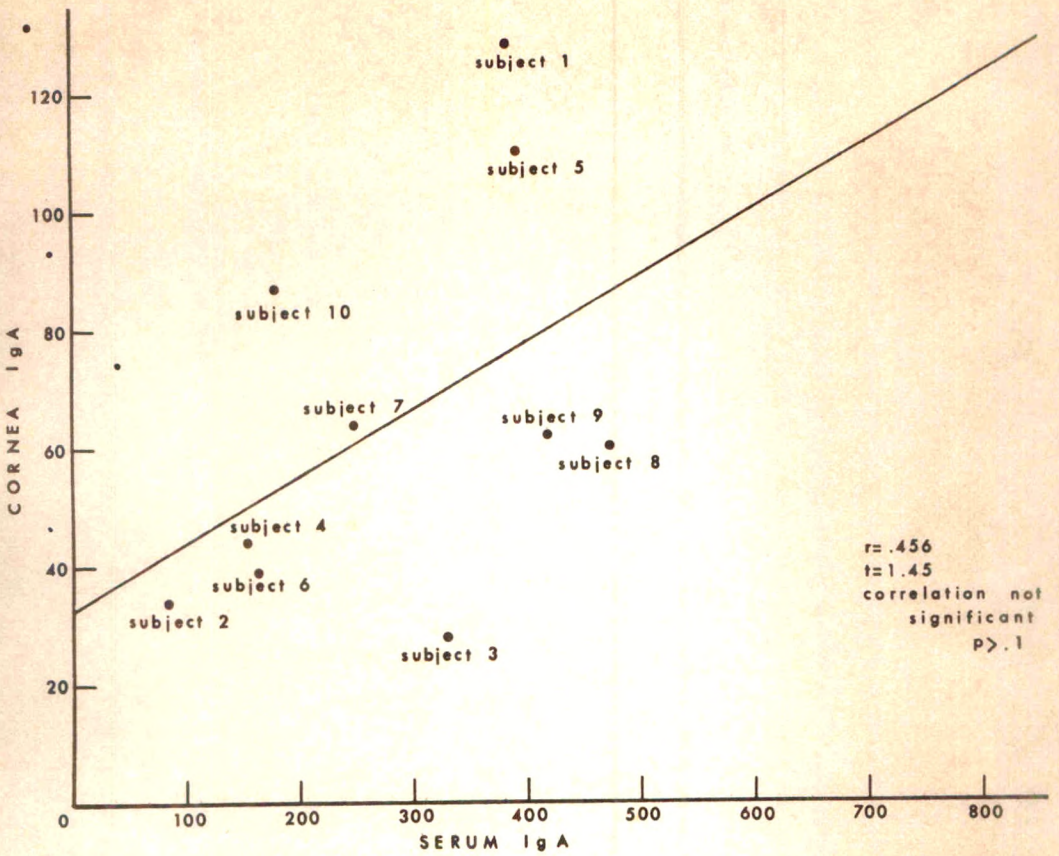


Fig. 7 (Allansmith and McClellan). Comparison of IgA (milligram per 100 milliliters) in corneas and sera of ten subjects.

($r = .56$, $P > .1$). Also, each eye with IgM in one cornea had IgM in the fellow cornea (Figs. 2 and 3) unrelated to serum levels (Figs. 2 and 3).

The capacity of the cornea for IgM is probably negligible except at the periphery. With the exception of one subject (Case 2), IgM was not found in the central cornea in this study ($P < .01$).

Albumin was consistently present throughout the cornea, as expected.[9] Less albumin was found in the central than in the peripheral cornea (Figs. 2 and 3). Maurice and Watson[9] postulated that albumin in rabbits came from the blood via the limbal vessels, diffused toward the central cornea and also out the posterior cornea through the endothelium. Our data support this concept. In rabbits, Maurice and Watson[9] found the peripheral-to-central ratio for albumin concentration was 3:1. In this study it was 3:1. The serum albumin to total corneal albumin ratio was 5:1 for rabbits and 5:1 for humans.

The distribution of a blood-derived solute across the cornea appears to be determined not only by the exclusion volume but also by the ratio of its loss across the endothelium to its rate of diffusion in the plane of the stroma.[5] Low molecular weight solutes pass readily across the endothelium and do not penetrate far in from the corneoscleral limbus. Larger molecules such as serum albumin are lost more slowly across the endothelium but penetrate relatively quickly in the stroma. Though they may penetrate to the apex of the cornea, they are present at a lower concentration in the

center than at the periphery. We anticipate that protein of even higher molecular weight, such as IgG and IgA, will pass even more slowly across the endothelium, will spread even further into the cornea, and may approximate a uniform concentration over the entire surface. Large molecules will penetrate only a short distance into the stroma, if at all, and will be absent from the central cornea.

Summary

We examined 20 corneas of ten subjects to determine the amounts and distribution of immunoglobulins and albumin. Immunoglobulins IgG and IgA were found in all corneas, were at the same level centrally and peripherally, and were at one-half and one-fifth the serum levels respectively. The amount of corneal IgG correlated with serum IgG, but not with IgA. Immunoglobulin IgM was present in five of the ten sets of eyes. No IgM was detected in the central buttons of four of the five sets where IgM occurred in the corneal periphery. Albumin was present in all corneas, but less centrally than peripherally. The cornea contains high levels of antibody proteins.

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EFFECTS OF DRUG VEHICLES ON OCULAR UPTAKE OF TETRACYCLINE

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Most antibiotics, whether in solution or suspensions, penetrate the anterior segment of the eye poorly when applied topically.[1] The ability of a drug to penetrate the eye in a topical medication is dependent on the rate of diffusion of the drug out of the vehicle and on the rate of penetration of the ocular barrier. This two-compartment diffusional process of drug release and tissue uptake is dependent on the physical properties of the drug, the barrier, and the vehicle. In this study, the drug vehicle containing tetracycline hydrochloride was altered so that the effect of each vehicle on the ocular uptake of tetracycline in rabbit eyes could be studied.

The role that the drug vehicle plays in ocular penetration of drugs depends on several factors. These include the diffusion of the drug out of the vehicle and the length of time that the vehicle-drug combination is in contact with the eye after topical administration. Studies using technetium Tc 99m to tag the vehicles of polyvinyl alcohol, alpha-methylcellulose, and ointment demonstrated that the corneal contact time of these vehicles was longer than that of isotonic saline.[2] It is this determination of vehicle corneal contact time that prompted a study of the influence that available ophthalmic vehicles have on the ocular uptake of tetracycline.

MATERIALS AND METHODS

One hundred ninety 3- to 5-kg New Zealand albino rabbits were lightly anesthetized by intravenously administering 3% pentobarbital sodium. The amount of anesthetic used was just enough so that the animals began moving their limbs in about 30 minutes. Additional small volumes of anesthetic were used to keep the animals from walking. Tetracycline labeled with tritium in various ophthalmic vehicles was dropped on the cornea and the eyelids were taped shut. We used isotonic saline, 1% alpha-methylcellulose, 1.4% polyvinyl alcohol, and a 6:4 mixture of white petrolatum-mineral oil ointment.

Two millicuries of tritiated tetracycline hydrochloride (1.4 curie/mM) powder was dissolved in 1 ml of isotonic saline. This stock solution in turn was divided into four equal parts which we added to each vehicle. Tetracycline hydrochloride was added to each of the four vehicles containing tritiated tetracycline to prepare vehicle concentrations of the drug of 0.01, 0.1, 0.25, 0.5 and 2.0%. The ointment-tetracycline preparation was dried in a vacuum to remove water and then the ointment was vigorously stirred. The homogeneity of the suspension of tetracycline hydrochloride crystals in the ointment was checked by examining a sample of the ointment with a light microscope.

Volumes of 0.005, 0.01, 0.05, and 0.1 ml of the tetracycline-vehicle preparation were placed on the rabbit corneas, and 15 minutes to eight hours later the rabbits were killed with an overdose of pentobarbital. The corneal epithelium was quickly denuded by swabbing with a cotton-tipped applicator that had been moistened with ethanol. After denuding the cornea, the applicator was placed in liquid scintillation vials. In quick succession, the eye was washed with 25 ml of isotonic saline and 0.02 ml of fluid was

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withdrawn from the anterior chamber. Next, a 7-mm diameter trephined corneal button was removed, and the lens extracted. The lens and cornea were both rapidly dipped four times in cold isotonic saline. The aqueous humor and tissues were prepared for liquid scintillation counting.[3] We compiled the results from each of three eyes except where indicated. Using *Escherichia coli* for the bio-assay, the therapeutic levels of tetracycline from the selected aqueous humor samples were determined by a microturbimetric method.[4]

Tritiated tetracycline-7 is prepared from 7-chlorotetracycline by catalytic halogen-tritium exchange. Its radiochemical purity by thin layer chromatography on silica gel in 10% citric acid saturated with n-butyl alcohol (butanol) was 95%. The purity by paper chromatography on Whatman P20 cellulose phosphate cation paper in 0.1% ammonium chloride was 93%. Examination of the chromatographic results on silica gel and cation paper with long-wavelength ultraviolet light showed that the tetracycline exhibited tailing. This is a well-known phenomenon with this compound, and as a result the radiochemical purity of tritiated tetracycline-7 is nearly 100%. The possibility that tritiated tetracycline-7 could have been altered during absorption in the eye was checked using aqueous humor samples taken from rabbits three and six hours after the conjunctival administration of 2% tetracycline hydrochloride in ointment. The samples were chromatographed on silica gel using 10% citric acid saturated in n-butyl alcohol and the radiochemical purity of these samples was greater than 90%.

Results

Between 15 minutes and six hours after topical administration of tritiated tetracycline, and irrespective of the vehicle, radioactivity was present in the aqueous fluid, cornea, lens, and corneal epithelium. The uptake of tritiated tetracycline did not increase linearly by increasing the volume of the vehicle applied to the eye from 0.005 ml to 0.1 ml, so the smaller volume was used for further experiments (Table 1). This volume was somewhat smaller than the tear volume of the human conjunctival sac which is approximately 0.007 ml.[5]

To determine the influence of the vehicle in prolonging the contact time of tritiated tetracycline on the eye, we used trace amounts, that is, micrograms, of the drug. In this way tissue saturation of the drug did not occur so the effect of each vehicle in supplying drug to the eye was determined. The concentrations of the antibiotic in the aqueous humor fluid are given in Figure 1. The aqueous vehicles resulted in lower levels of tritiated tetracycline and shorter durations than found with the ointment vehicle. The peak values of tetracycline in the vehicles other than saline were around one hour, with the levels approximately the same 30 minutes and three hours later.

Thirty minutes after the ocular administration of 0.1, 0.25, 0.50, and 2.0% tetracycline contained in the saline, methylcellulose, polyvinyl alcohol, and ointment ve-

TABLE 1

TETRACYCLINE CONCENTRATION IN RABBIT AQUEOUS HUMOR 30 MINUTES AFTER TOPICAL APPLICATION OF FOUR VOLUMES OF 2.0% ANTIBIOTIC TO SIX EYES*

Vehicles	0.005 ml	0.01 ml	0.05 ml	0.01 ml
Isotonic saline	0.27(0.14–0.33)	0.42(0.30–0.56)	0.80(0.71–0.98)	0.72(0.66–0.82)
Polyvinyl alcohol	0.28(0.22–0.35)	0.40(0.27–0.58)	0.40(0.32–0.55)	0.65(0.48–0.76)
Methylcellulose	0.33(0.17–0.42)	0.48(0.36–0.73)	0.60(0.53–0.77)	0.68(0.55–0.91)
Ointment	9.2(7.9–11.3)	8.7(7.7–10.8)	10.5(8.2–12.0)	10.2(9.3–11.1)

* Values given as mean and (range) in milligrams per liter.

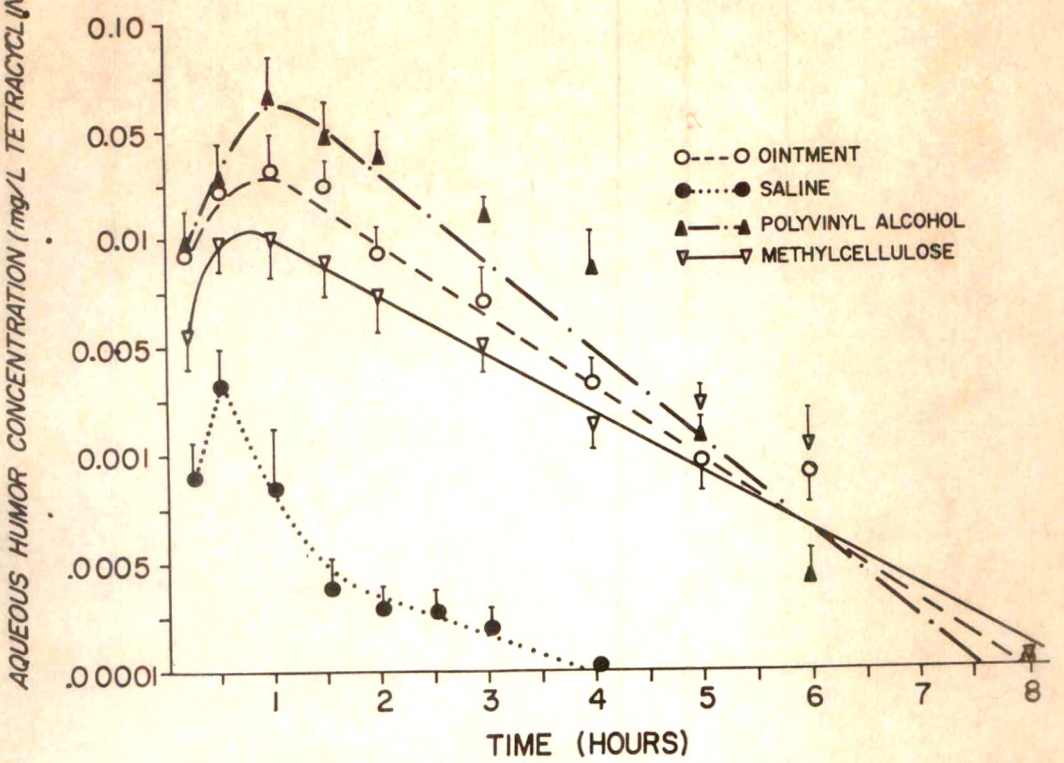


Fig. 1 (Hardberger, Hanna, and Goodart). Trace amounts of tritiated tetracycline hydrochloride (0.1 mg/ml) in the drug vehicles of ointment, isotonic saline, 1.4% polyvinyl alcohol, and 1% alpha-methylcellulose were applied in a volume of 0.005 ml to the rabbit eye and then patched. The values are the mean of six eyes, and the bars are the plus or minus value of the standard error of the mean.

hicles, the drug levels in the aqueous humor were determined (Fig. 2). Concentrations of tetracycline in 0.25% saline or greater gave results similar to those found by using methylcellulose and polyvinyl alcohol. None of the aqueous vehicles resulted in antibacterial aqueous humor levels of tetracycline. However, antibacterial levels of tetracycline in the aqueous humor were produced by the use of 0.5 and 2.0% tetracycline hydrochloride in ointment.

Tetracycline hydrochloride in water or tears autofluoresces when exposed to long-wavelength ultraviolet light. The minimum concentration of tetracycline in the tear film by direct observation of the rabbit was 10 mg/liter. By opening the rabbit eye at various intervals after the topical administration of tetracycline in one of the vehicles and directing ultraviolet light on the eye, we made an estimate of the rate of drug loss from the tear film. Tear film levels of the drug decreased rapidly after the application of 2.0% tetracycline in saline. Some of the drug appeared to be in a precipitated form in the mucin on the conjunctiva at 15 minutes, but there was no detectable concentration of tetracycline in the tear film at that time. On the contrary, the tear film concentration of drug was detectable two hours after the application of 2.0% tetracycline in ointment. We detected the drug concentrations for 2.0% tetracycline in the polyvinyl alcohol and methylcellulose vehicles in the tear film one hour later but not at two hours.

We studied the influence of the rapid decline in tetracycline concentration in the

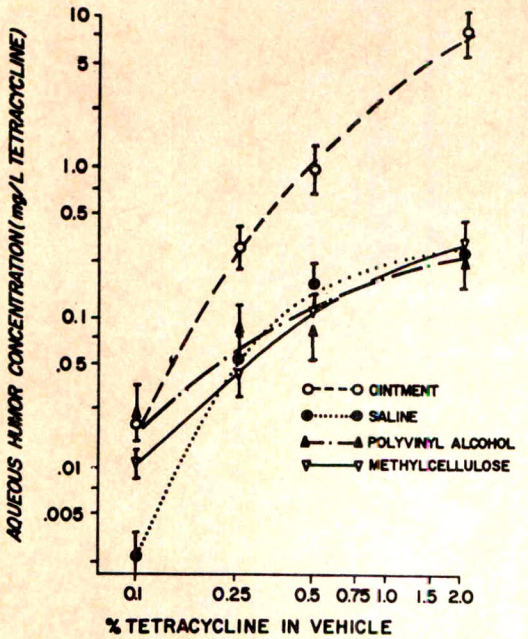


Fig. 2 (Hardberger, Hanna, and Goodart). Various concentrations of tritiated tetracycline in the vehicles are plotted against the aqueous humor concentrations of tetracycline at 30 minutes after topical application to rabbit corneas and the eyes patched. The tetracycline concentrations in the aqueous humor (mean of six eyes, standard error of the mean indicated by bars) and the vehicle are plotted on a log scale.

tear film after using the drug in saline on the ocular tissue levels of the antibiotic by sampling the surface of the cornea, the cornea, the aqueous humor, and the lens at 30 minutes and three hours. The data obtained using two time intervals, four vehicles, four concentrations of drug, and four tissue or fluid samples are presented in Table 2. Only methylcellulose and ointment showed a concentration of 1 mg/liter of tetracycline in the aqueous humor at 30 minutes and three hours. A comparison of the ocular levels of tetracycline for the four vehicles at 30 minutes and at three hours showed the drug rapidly leaving the surface of the cornea and the epithelium, but not the remainder of the cornea. However, 2.0% tetracycline in ointment was the only vehicle that maintained aqueous humor levels of the drug over 1 mg/liter for three hours.

Four percent nonradioactive tetracycline hydrochloride in ointment was applied to the conjunctival sac of four rabbit eyes. Aqueous humor samples were removed 30 minutes later. The aqueous humor had a yellowish tinge and fluoresced yellow to long-wavelength ultraviolet light. These aqueous humor samples were bacteriostatic to sensitive strains of *E. coli.*[4] Also, samples of aqueous humor from four rabbits taken 30 minutes after the conjunctival application of nonradioactive 2.0% tetracycline hydrochloride in ointment were bacteriostatic to *E. coli.* The tritiated tetracycline-7 from rabbit aqueous humor samples taken three hours after the conjunctival application of 2.0% tritiated tetracycline hydrochloride in ointment was subjected to paper chromatography. The radioactive purity of the tritiated tetracycline was an average of 91%. These studies indicated that the results using tritiated tetracycline (Tables 1 and 2) represent only tetracycline hydrochloride concentrations.

Light microscopic examination of the ointment preparations of tetracycline hydrochloride, available commercially for ocular use, revealed small crystals of the drug. The tetracycline hydrochloride did not dissolve in the ointment and the drug crystals were separated out by heating to 50°C. When these preparations were placed into rabbit eyes, we saw that the yellow crystals of the drug were initially in contact with the corneal and conjunctival surface, by slit-lamp examination. Four rabbits were treated in both eyes with topical 2.0% tetracycline hydrochloride in ointment daily for 14 days. There was no slit-lamp or histologic evidence of damage to the corneal or conjunctival epithelium when this concentration of drug was applied four times daily for 14 days. However, 4.0 and 10% tetracycline hydrochloride in ointment applied to the rabbit eye in this manner produced an inflamed eye by seven days that lasted two

TABLE 2

CONCENTRATION OF TETRACYCLINE IN PARTS OF THE RABBIT EYE AS INFLUENCED BY THE CONCENTRATION OF DRUG APPLIED, THE VEHICLE EMPLOYED,* AND THE TIME OF SAMPLING†

Concentration, %	Vehicle	Swab	Cornea	Aqueous Humor	Lens
		30-Minute Samples			
0.1	Isotonic saline	0.04 (0.09–0.01)	0.011 (0.004–0.023)	0.001 (0.000–0.002)	0.004 (0.002–0.006)
	PVA	0.12 (0.09–0.42)	0.039 (0.027–0.50)	0.022 (0.017–0.029)	0.007 (0.003–0.008)
	MC	0.71 (0.57–0.95)	0.043 (0.033–0.056)	0.017 (0.014–0.022)	0.005 (0.003–0.007)
	Ointment	0.64 (0.43–0.88)	0.049 (0.037–0.062)	0.018 (0.014–0.027)	0.008 (0.002–0.013)
0.25	Isotonic saline	0.18 (0.10–0.23)	0.069 (0.056–0.74)	0.053 (0.037–0.068)	0.009 (0.005–0.014)
	PVA	0.27 (0.24–0.35)	0.13 (0.11–0.19)	0.074 (0.070–0.088)	0.010 (0.007–0.018)
	MC	1.31 (1.27–1.50)	0.083 (0.043–0.16)	0.049 (0.031–0.055)	0.046 (0.029–0.051)
	Ointment	7.97 (6.36–9.09)	0.68 (0.57–0.81)	0.41 (0.33–0.52)	0.062 (0.048–0.071)
0.50	Isotonic saline	0.33 (0.23–0.41)	0.22 (0.16–0.33)	0.062 (0.047–0.077)	0.017 (0.013–0.022)
	PVA	0.32 (0.30–0.39)	0.11 (0.08–0.13)	0.071 (0.066–0.081)	0.010 (0.084–0.022)
	MC	2.52 (2.02–3.19)	0.12 (0.10–0.15)	0.18 (0.09–0.26)	0.053 (0.047–0.059)
	Ointment	170 (157–182)	2.37 (2.02–2.49)	0.95 (0.89–1.22)	0.19 (0.12–0.27)
2.0	Isotonic saline	0.59 (0.42–0.71)	0.28 (0.19–0.37)	0.25 (0.18–0.29)	0.043 (0.031–0.057)
	PVA	0.43 (0.29–0.50)	0.44 (0.30–0.53)	0.21 (0.11–0.37)	0.071 (0.063–0.088)
	MC	6.77 (6.33–7.18)	0.46 (0.33–0.59)	0.36 (0.33–0.41)	0.11 (0.09–0.14)
	Ointment	360 (199–410)	15.7 (13.2–16.5)	9.41 (8.14–10.3)	0.42 (0.31–0.57)
		3-Hour Samples			
0.1	Isotonic saline	0.001 (0.000–0.003)	0.051 (0.029–0.072)	0.005 (0.001–0.008)	0.003 (0.002–0.005)
	PVA	0.001 (0.009–0.003)	0.066 (0.042–0.071)	0.008 (0.003–0.017)	0.006 (0.004–0.011)
	MC	0.002 (0.001–0.003)	0.088 (0.048–0.110)	0.012 (0.007–0.029)	0.005 (0.003–0.012)
	Ointment	0.004 (0.001–0.006)	0.13 (0.094–0.149)	0.016 (0.009–0.021)	0.010 (0.007–0.019)
0.25	Isotonic saline	0.003 (0.001–0.005)	0.16 (0.09–0.22)	0.023 (0.015–0.035)	0.009 (0.004–0.018)
	PVA	0.003 (0.001–0.004)	0.29 (0.11–0.37)	0.036 (0.029–0.047)	0.007 (0.003–0.012)
	MC	0.008 (0.002–0.011)	0.46 (0.29–0.55)	0.044 (0.028–0.053)	0.007 (0.002–0.014)
	Ointment	0.091 (0.001–0.15)	0.91 (0.82–1.12)	0.16 (0.088–0.21)	0.041 (0.009–0.066)
0.50	Isotonic saline	0.016 (0.003–0.033)	0.33 (0.27–0.48)	0.62 (0.031–0.14)	0.002 (0.000–0.003)
	PVA	0.008 (0.002–0.011)	0.51 (0.39–0.62)	0.063 (0.043–0.10)	0.014 (0.007–0.024)
	MC	0.013 (0.003–0.034)	0.97 (0.77–1.18)	0.097 (0.055–0.15)	0.009 (0.003–0.015)
	Ointment	0.26 (0.013–0.31)	2.81 (1.92–3.12)	0.52 (0.19–0.73)	0.028 (0.013–0.042)
2.0	Isotonic saline	0.003 (0.001–0.004)	0.34 (0.23–0.51)	0.31 (0.17–0.46)	0.003 (0.001–0.004)
	PVA	0.005 (0.001–0.007)	0.61 (0.53–0.79)	0.21 (0.13–0.33)	0.022 (0.018–0.027)
	MC	0.020 (0.008–0.038)	1.63 (1.13–2.03)	0.35 (0.27–0.49)	0.019 (0.009–0.033)
	Ointment	0.44 (0.09–0.63)	3.41 (2.73–4.57)	1.23 (0.72–1.92)	0.13 (0.091–0.22)

* PVA indicates polyvinyl alcohol; MC, methylcellulose.
† Values given as mean and (range) of samples in milligrams per liter from three eyes; six eyes in aqueous humor samples.

days after discontinuance of the medication.

DISCUSSION

It is well documented that tetracycline does not readily penetrate into the anterior segment of the normal eye in antibacterial concentrations. Douvas, Featherstone, and Braley[6] bathed the rabbit eye with an aqueous solution of 0.5% tetracycline. They failed to detect antibacterial concentrations of the drug at any time in the aqueous humor unless the cornea was first abraded. Cannon, Nichols, and Leopold[7] used 1.0 and 3.0% tetracycline ointment in the rabbit eye. They also failed to detect the drug in the aqueous humor. Thus, high doses of the drug were administered systemically, that is, 7 to 50 mg/kg intravenously to produce bacteriostatic concentrations of tetracycline in the aqueous humor of the human or rabbit eye.[7-10]

The antibacterial concentration of tetracycline in saline solution is approximately 1 mg/liter for most susceptible pathogens. Since aqueous humor normally contains less protein than plasma, the protein binding of tetracycline by the aqueous humor is minimal. We were able to achieve this level of

tetracycline in the anterior segment of the rabbit eye by employing several experimental design factors. We found the tetracycline irritating in concentrations of 0.5, 1.0, and 2.0% in various vehicles. Similarly, the rabbits rubbed their eyes after we applied tetracycline. When the volume of 2.0% tetracycline applied to the conjunctival sac was 0.005 ml or less, the irritation and lacrimation were minimal. Also, our previous study indicated that ophthalmic vehicles of polyvinyl alcohol methylcellulose, and ointment lengthen the contact time of Tc 99m chloride with the eye, especially when both eyes were closed.[3] Further, the maximum volume of vehicle retained by the human eye without loss on the eyelids was about 0.005 ml.[5] In the experimental design using rabbits, the vehicle was applied in a volume of 0.005 ml, the eyelids taped shut, and the animals lightly anesthetized to avoid rubbing the eyes. Under these conditions, the single application of 2.0% tetracycline in ointment yielded antibacterial concentrations of drug in the anterior segment of the eye for any length of time.

The ointment vehicle appears to be a special case of drug delivery to the eye. Antibacterial agents such as tetracycline hydrochloride, chloramphenicol, sulfacetamide sodium, phenylmercuric nitrate, and thimerosal are all suspended in ointment. On blinking, the ointment vehicle breaks up into small droplets and the antibacterial drug crystals are liberated. These crystals remain in contact with the cornea and conjunctiva until they dissolve. This acts as a drug depot for ocular delivery especially when higher concentrations of drug suspensions in the ointment are used. Unfortunately, there appears to be a limit to the amount of tetracycline hydrochloride that can be used due to a foreign body reaction to the needle form of the crystals. Antibacterial drugs dissolved in an aqueous vehicle are readily diluted by the tears and washed into the punctum.

Summary

Varying concentrations of tetracycline hydrochloride were topically applied to the rabbit eye in several ophthalmic vehicles. The antibiotic levels in the corneal epithelium, aqueous humor, and lens were markedly elevated by increasing the drug concentration and the drug contact time with the eye. The ocular levels of tetracycline were increased by the vehicle in this ascending order: isotonic saline, 1.4% polyvinyl alcohol, 1% alpha-methylcellulose, and a 6:4 mixture of white petrolatum-mineral oil ointment. Tetracycline hydrochloride as a 2.0% suspension in ointment produced anterior chamber and corneal concentrations for several hours in the range of bacteriostasis for many gram-negative bacteria that occasionally invade the eye.

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BIOCHEMICAL ASPECTS OF CONTACT LENS WEAR

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Some biochemical changes in the corneal epithelium as a result of contact lens wear have been thought to be secondary to anoxia. For example, the epithelial edema seen after prolonged wearing of poorly fitted lenses is a well-recognized indicator of cellular dysfunction. Glycogen depletion[1-4] and changes in adenosine triphosphate (ATP) levels[3] have been used as indicators of the adequacy of oxygenation under lenses. Burns, Robert, and Rich[3] supported this association of glycogen depletion with anoxia by showing no glycogen fall under oxygen permeable lenses such as silicone lenses. Conversely, Hill, Augsburger, and Uniacke[5] showed that although the glycogen depletion under conventional hard lenses was more pronounced, glycogen levels in epithelium underlying silicone lenses were still only about 80% of normal. Although oxygenation under lenses is necessary for the maintenance of glycogen stores, such results would indicate that adequate oxygenation may not be sufficient, by itself, to protect the glycogen level.

Previous experiments in our laboratory indicated that epithelial trauma alone may lead to epithelial glycogen mobilization.[6] Our purpose here is to confirm the changes in glycogen content that occur under contact lenses in rabbits, and to relate these changes to hydration, adenosine phosphate content, and alterations in anaerobic and aerobic enzyme activity. The effect of minor trauma on rabbit corneal epithelium glycogen stores was also evaluated.

From the Department of Cornea Research, Eye Research Institute of Retina Foundation, Boston, Massachusetts. This study was supported by research grant EY-00208 and training grant EY-00043 from the National Eye Institute; in part by a Fight for Sight, Inc., grant-in-aid, G-495 (Dr. Thoft); and in part by the Massachusetts Lions Eye Research Fund, Inc.

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The results indicate that glycogen is mobilized when contact lenses are applied to the eye, even after prolonged adaptation, and that the epithelium does not return to normal under lenses despite long periods of wear. Furthermore, the glycogen is mobilized in response to trauma even in the presence of adequate oxygenation. There were no significant changes in enzymes of the anaerobic glycolytic or tricarboxylic acid pathways. The ATP content of the epithelium, however, was depleted parallel to the depletion of glycogen stores and to the development of edema, indicating that the edema is probably the result of inadequate metabolic energy. While inadequate oxygenation probably always leads to edema, edema should not always be taken as a sign of inadequate oxygenation.

MATERIALS AND METHODS

Animal studies—Rabbits weighing between 2.5 and 3.5 kg were used in all experiments. Conventional methyl methacrylate, hard contact lenses, polymacon (Soflens), crofilcon A (CS-151), and silicone lenses were used. The hard and soft lenses were 13 mm in diameter and 0.5 mm thick. The crofilcon A lenses were 13 mm in diameter and varied in thickness, 0.07, 0.3, or 0.6 mm thick. The polymacon and crofilcon A are both hydrogel lenses. They are both relatively permeable to oxygen; the thinnest one (for example, crofilcon A, 0.07 mm) is the most permeable. The silicone lenses were simple silicone membranes, 7 mm in diameter and 0.12 mm thick. Both the crofilcon A and silicone lenses are oxygen permeable. All lenses had a radius of curvature of 7.5 mm.

After the lenses were worn for six or 18 hours, either after adaptation or without it, the rabbits were anesthetized with pentobarbital sodium. Epithelia that were to have enzyme or glycogen levels (micromoles

TABLE 1

GLYCOGEN LEVELS AND HYDRATION OF RABBIT CORNEAL EPITHELIUM AFTER CONTACT LENS WEAR*

Lens Type, Thickness, mm	Adaptation Time (days)/ Wearing Time (hrs)	Glycogen	P<	Hydration	P<
None	—	239 ± 11 (11)	—	3.11 ± 0.22 (11)	—
Methyl methacrylate, 0.5	0/1	199 ± 6 (6)	—	2.78 ± 0.44 (6)	—
Methyl methacrylate, 0.5	0/6	92 ± 12 (10)	.001	3.77 ± 0.16 (10)	.01
Methyl methacrylate, 0.5	0/18	60 ± 6 (8)	.001	4.09 ± 0.12 (8)	.0027
Methyl methacrylate, 0.5	5/6	43 ± 2 (6)	.001	3.12 ± 0.17 (6)	—
Methyl methacrylate, 0.5	11/6	66 ± 7 (13)	.001	3.48 ± 0.09 (13)	—
Methyl methacrylate, 0.5	26/6	61 ± 8 (8)	.001	3.03 ± 0.13 (8)	—
Crofilcon A, 0.07	0/6	119 ± 12 (6)	.001	2.91 ± 0.25 (6)	—
Crofilcon A, 0.30	0/6	117 ± 16 (5)	.001	3.30 ± 0.45 (5)	—
Crofilcon A, 0.60	0/6	100 ± 12 (6)	.001	2.92 ± 0.19 (6)	—
Polymacon, 0.5	0/6	112 ± 18 (3)	.001	—	—
Silicone, 0.12	0/6	174 ± 17 (4)	.01	3.25 ± 0.27 (4)	—

* Values are expressed as averages followed by the standard errors of the mean (±) with the number of determinations in parentheses. The P value is given if the value was significantly different from normal by the Student's t-test.

per gram of dry weight) measured were scraped off, using a No. 15 blade. They were then frozen, weighed, freeze-dried, and reweighed. From these weights, an estimate of the hydration (milligrams of water per milligram of dry weight) could be made. Epithelium used for adenosine phosphate analyses was frozen in situ with a molded metal block, previously cooled in liquid nitrogen. The eye was then enucleated and the whole eyeball frozen and freeze-dried. The dried epithelium was scraped off as a powder and weighed as described previously.[7]

Adaptation to the unfitted hard contact lenses consisted of gradually increasing the wearing time from one hour the first day to six hours the last, over a period of five, 11, or 26 days.

Trauma to the epithelium was produced by gently rubbing the epithelial surface with a cotton swab moistened with artificial tear solution[8] for one minute while the rabbits were under pentobarbital sodium anesthesia. No local anesthetics were used. Fluorescein staining, immediately afterward, showed no detectable changes. Immediately, or 15, 30, 60, or 90 minutes afterward, during which time no attempt was made to keep the eyelids closed, the epithelium was recovered as described, and hydration and glycogen or ATP were measured. Several eyes were enucleated immediately after the rubbing for histologic examination.

Chemical analyses—Glycogen was measured in glucose units after precipitation with ethanol and hydrolysis in 2N sulfuric acid for 90 minutes.[9] The glucose was then measured by using the hexokinase reaction. We measured the glycolytic and tricarboxylic acid cycle enzyme levels after extraction in phosphate buffer by freeze-thawing, using enzymatic optical tests according to the methods of Bücher, Luh, and Pitte.[10] Phosphorylase was measured enzymatically according to the method of Jones and Wright.[11] All enzyme activities were expressed as international units per gram of protein. Protein was determined by the Lowry method.[12] Adenosine triphosphate was measured by the firefly luminescence method[13] and adenosine diphosphate (ADP) by enzymatic optical tests according to Hohorst, Kreutz, and Bücher[14] after extraction in 0.5N perchloric acid and neutralization.

RESULTS

There was a fall in glycogen and increase in hydration that occurred after unfitted hard

TABLE 2

ADENOSINE TRIPHOSPHATE AND ADENOSINE DIPHOSPHATE IN RABBIT CORNEAL EPITHELIUM AFTER CONTACT LENS WEAR*

Duration of Methyl Methacrylate Contact Lens Wear, hrs	ATP	% of Normal	ADP	% of Normal	ATP/ADP Ratio	No. of Determinations
0	12.3±0.5	—	3.1±0.4	—	6.0±0.9	19
1	12.2±0.6	99	3.9±0.7	126	3.8±0.8	6
6	8.9±0.9	75	3.6±0.4	106	2.7±0.5	7
18	7.4±0.6	62	4.2±0.5	124	1.8±0.2	8

* Values are expressed as standard error of the mean (±).

contact lenses were worn for six or 18 hours by rabbits (Table 1). Even after a slow increase in wearing time, with six hours of wear after five, 11, or 26 days, there was no preservation of epithelial glycogen stores. Glycogen recovery times were prompt in unadapted eyes, with 50% recovery after two hours and up to 85% recovery after 24 hours.

Soft contact lenses were also placed on the cornea for six hours, but no adaptation was done. The glycogen level fell to about 60% of normal under the polymacon unit. Crofilcon A, which is relatively oxygen permeable,[15] showed a substantial fall of glycogen to 60% of normal with the 0.07-mm thick lens. Thicker lenses (0.6 mm) showed drops to 42% of normal after six hours of wear. The silicone lenses, 0.12 mm thick and only 7 mm in diameter, also showed a fall in glycogen levels to about 73% of normal. If hard lenses were left on the eyes more than

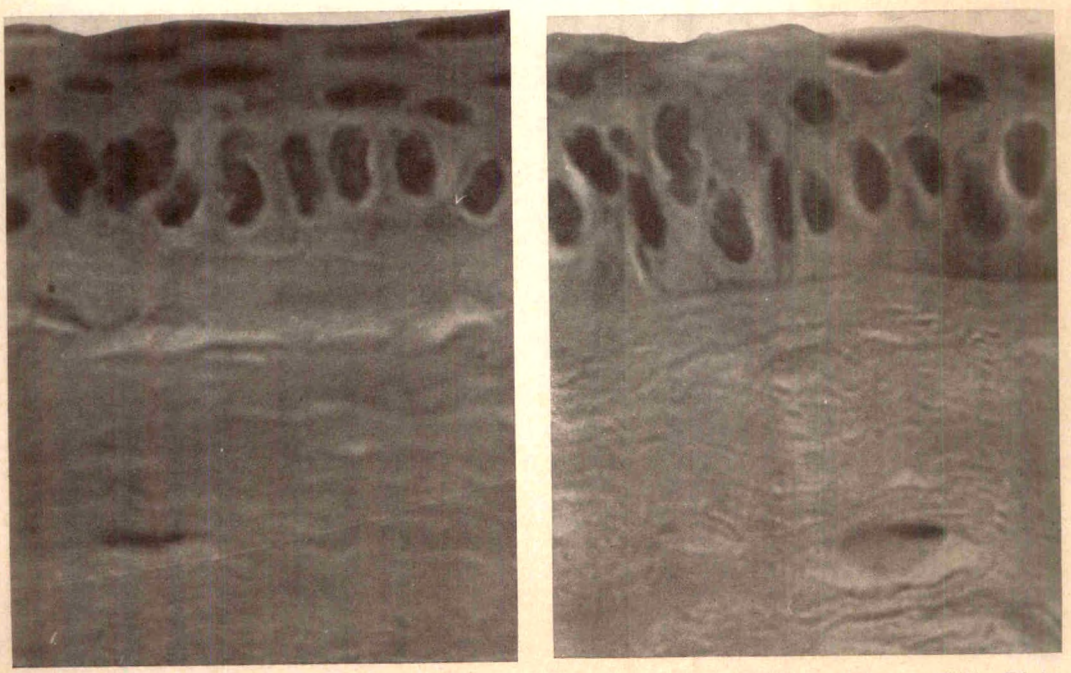


Fig. 1 (Thoft and Friend). Left, Normal corneal epithelium (hematoxylin and eosin, ×550). Right, Corneal epithelium after a one-minute rubbing with a moist cotton swab shows a loss of the superficial cell layer and some enlargement of cells in the lower layers (hematoxylin and eosin, ×550).

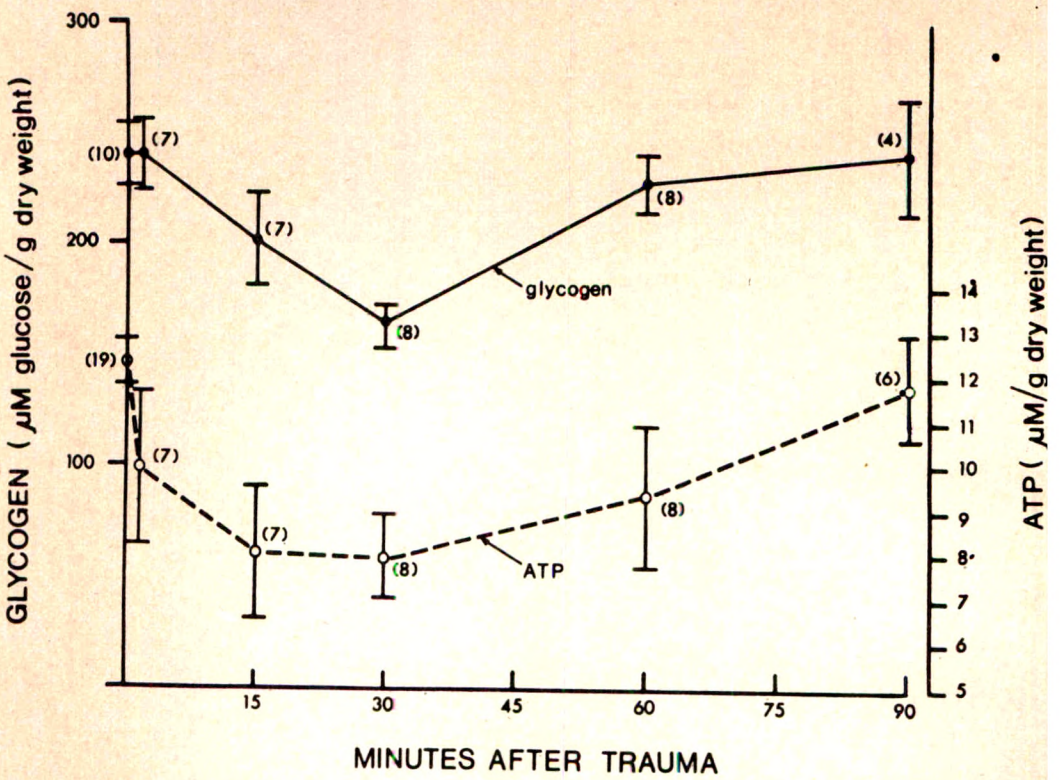


Fig. 2 (Thoft and Friend). Rabbit corneal epithelial glycogen and adenosine triphosphate (ATP) were reduced 30 minutes after rubbing with a moist cotton swab, but returned to normal after 1½ hours.

ten hours, epithelial defects occurred and did not heal unless the lens was removed.

The ATP and ADP levels and the ATP/ADP ratio found after hard contact lens wear were compiled (Table 2). After 18 hours in the unadapted state, the ATP levels were significantly reduced. Significant changes in ATP levels paralleled similar changes in hydration and glycogen content (Table 1).

Histologic examination of eyes removed immediately after rubbing the epithelial surface with a cotton swab for one minute showed that the superficial layer of epithelial cells had been removed and that the columnar cells were slightly enlarged (Fig. 1).

This trauma to the epithelial surface caused a reduction in epithelial glycogen and ATP to 70% of normal in 30 minutes, with full recovery to normal after 90 minutes (Fig. 2). There was an increase in hydration caused by trauma (Fig. 3), suggesting that the ATP levels were even lower than indicated by the absolute decrease. Both glycogen and hydration returned to normal before the ATP levels did.

Phosphorylase, hexokinase, lactate dehydrogenase, pyruvate kinase, malate dehydrogenase, and glucose-6-phosphate dehydrogenase levels were not affected by six-hour contact lens wear (Table 3).

Discussion

Contact lens wear apparently involves two separate mechanisms, anoxia and trauma, that may cause corneal edema. Cornel epithelial edema resulting from anoxia has been well known since the original work of Smelser and Ozaniks[1] and was recently documented by Uniacke and coworkers.[16] The occurrence of edema after relatively minor epithelial trauma had not previously been noted, however, although

earlier experiments in our laboratory indicated that glycogen stores were sensitive to trauma.[6] The current experiments not only confirm the fact that trauma reduces epithelial glycogen stores, but this reduction is accompanied by a significant increase in hydration, a measure of edema. This association of trauma with reduced glycogen stores and ATP levels is important in the consideration of the pathophysiology of several disease states. For example, any condition associated with chronic trauma, such as entropion, trichiasis, or contact lens wear, may disturb the integrity of epithelial cells to the extent that substantially greater amounts of metabolic energy are necessary for the preservation of an intact epithelial layer. Distortion of epithelial cells may lead to significant alteration in ion fluxes so that energy is not only expended for repair of damaged cell structures, but it is also needed for greatly increased cation pumping. While the glucose flux from the anterior chamber to the corneal epithelial surface is five times greater than the amount of glucose consumed by undisturbed epithelial cells (in the rabbit),[6] traumatized cells undergo rapid mobilization of glycogen and still show a significant drop in ATP levels. Although ATP levels are sensitive to the method of epithelial tissue preparation,[17] we found they are relatively resistant to changes that do not involve physical contact to epithelium, such as moist chamber storage (unpublished data). Changes of the degree found after trauma in the present experiments may be a prelude to epithelial cell death.

The role of anoxia as a factor leading to

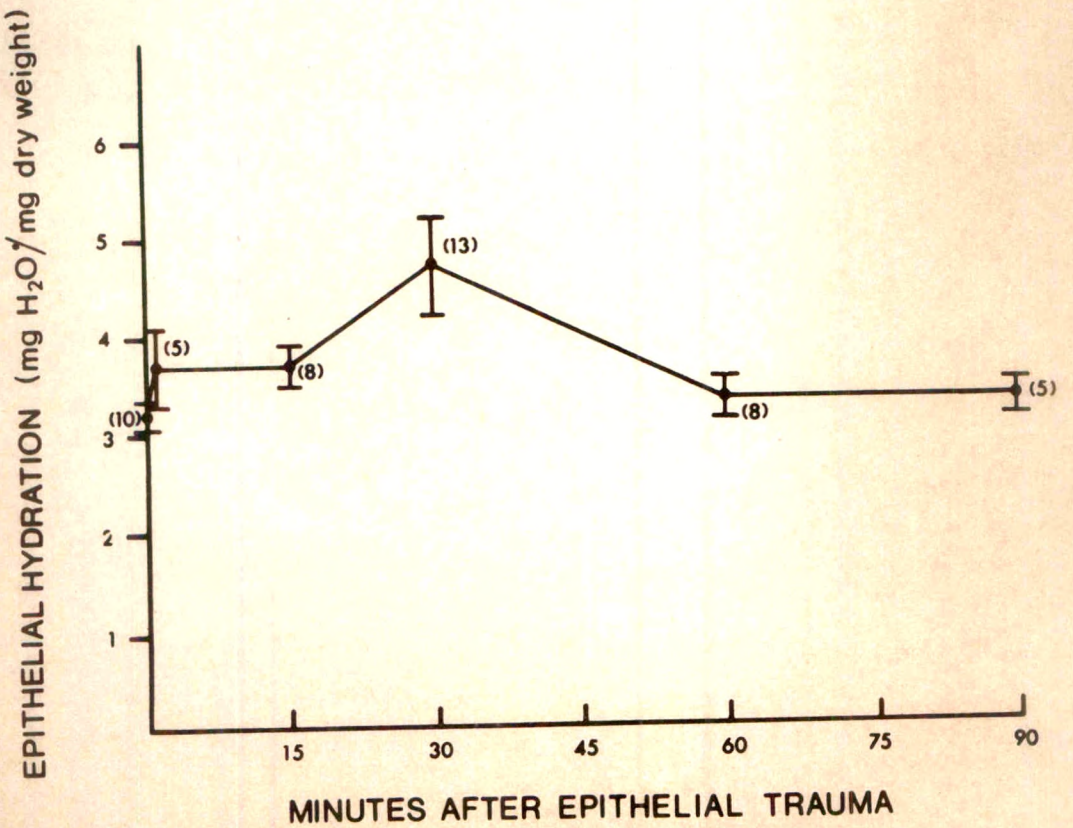


Fig. 3 (Thoft and Friend). Rabbit corneal epithelial hydration was increased 30 minutes after rubbing with a moist cotton swab and had returned to normal after one hour.

TABLE 3

CORNEAL EPITHELIAL ENZYME LEVELS AFTER 6 OR 19 HOURS OF METHYL METHACRYLATE CONTACT LENS WEAR*

Enzyme	Normal	6 Hrs	19 Hrs
Hexokinase	10.2±1.4 (7)	9.1±2.0 (5)	10.7±0.9 (9)
Glucose-6-phosphate dehydrogenase	66.0±4.9 (7)	80.6±4.9 (5)	81.4±6.6 (9)
Lactate dehydrogenase	20,700±2,960 (7)	16,200±1,760 (5)	22,800±3,800 (9)
Pyruvate kinase	159±32 (7)	86±21 (5)	149±21 (9)
Malate dehydrogenase	402±32 (7)	359±27 (5)	523±110 (9)
Phosphorylase	28±5 (6)	33±2 (9)	—

* Enzyme levels are expressed in International Units at 24°C/g of protein followed by the standard errors of the mean (±) with the number of determinations in parentheses.

glycogen depletion, ATP loss, and edema in contact lens wear has received considerable attention.[3,5,18] While Burns, Robert, and Rich[3] found that glycogen stores were normal under oxygen-permeable silicone lenses, our experiments do not confirm this. Our findings, and those of Hill, Augsburger, and Uniacke,[5] show that oxygen permeable lenses are associated with a 20% reduction in glycogen stores. These results are consistent with our thesis that trauma alone may be responsible for a significant metabolic alteration in epithelial cells. Rubbing of the epithelial cells does not interfere with oxygenation, yet the layer becomes edematous and significantly depleted of glycogen and ATP. The search for the ideal contact lens, then, is not only directed by the requirement for oxygen permeability, but by the need for a nontraumatic apposition to the cornea. Such a combination may be best approximated in soft, gas-permeable polymers that do not move on the cornea.

If corneal glucose supplies are in excess, one can ask why glycogen stores fall, why ATP levels fall, and why edema occurs in the presence of anoxia or trauma. The enzymatic levels of the anaerobic glycolytic mechanisms apparently do not respond to utilize the greatly increased amount of glucose required to produce the same amount of ATP. There is no evidence that the activities of hexokinase, glucose-6-phosphate dehydrogenase, and other enzymes change in response to contact lens wear and to the amount of anoxia or trauma introduced by the lenses. Possibly, these enzymes are initially present in great excess, so that induction of increased activity would not be expected. If the corneal epithelium is analogous to the crystalline lens,[19] however, hexokinase may, in fact, be the limiting factor in glucose utilization. The role of hexokinase in epithelial glucose utilization must be clarified before it can be assumed that anoxia and trauma cause edema by exceeding the ability of the epithelial cells to create ATP from the anaerobic breakdown of glucose.

SUMMARY

Glycogen, adenosine triphosphate, and hydration were measured in rabbit corneal epithelium to determine whether the corneal epithelium glycogen decrease, increase in epithelial hydration, and decrease in epithelial adenosine triphosphate stores, seen as a result of contact lens wear, were secondary only to anoxia or may also have resulted from mild trauma, with no interference to oxygenation. Conventional contact lens wear, trauma, and oxygen-permeable contact lens wear caused metabolic changes, showing trauma as well as anoxia may play an important role in the corneal epithelial response to contact lens wear.

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CRYPTOPHTHALMOS SYNDROME WITH BASAL ENCEPHALOCELES

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Cryptophthalmos can occur as an isolated anomaly, but usually it is associated with multiple malformations that constitute the cryptophthalmos syndrome, that is, malformation of the ear and nose, cleft lip and palate, syndactyly, and urogenital anomalies. We present a case of two basal encephaloceles in a patient.

CASE REPORT

This white girl, the child of healthy, unrelated parents, was born April 14, 1971, weighing 2,144 g (6 lb 2 oz). The pregnancy and delivery were uneventful. Multiple facial anomalies were noted at birth and, seven days later, right craniofacial dysplasia with absence of the right ear and eye, cleft lip and palate, and a congenital heart defect with congestive heart failure were diagnosed. An intravenous pyelogram demonstrated normal kidneys and urinary tract, and chromosomal studies were normal. The heart defect was later evaluated with cardiac catheterization and angiography, revealing ventricular and atrial septal defects, tricuspid atresia, detransposition of the great vessels, right aortic arch, and aberrant right subclavian artery. Parenchymal lung disease was found also.

Her development was somewhat slow. She began to walk at 2 years of age and still did not talk when we saw her eight months later.

Examination showed that the right side of her head and face were hypoplastic, the right external ear was totally missing, and the right orbit, eyelids, and eye were rudimentary (Figs. 1 and 2). A soft mass bulged on the right side of the nose; she had a repaired median cleft lip and a cleft palate. The eyelids on the right side were small, but the cilia were well formed; while crying, she had tears in both eyes. The eyebrow seemed to bifurcate toward the nose, and it was not continuous with the hairline. There was a shallow depression between the rudimentary eyelids. The right orbit was small, and a small bud of tissue could be palpated through it. The child had the habit of stabbing her finger into the right eye region. No light-sensitive tissue on that side could be demonstrated by bright lights. On the left side the ocular examination was completely normal.

The head circumference was 45.3 cm, which was on the second percentile of the Nellhaus chart. There was no evidence of syndactyly or genital anomalies. The child had coordinated movements, walked properly, and had no gross neurologic defects. She seemed to understand but could utter only single, barely intelligible words.

No other congenital malformations were known to have occurred in the family. A 9-month-old brother was normal, and the mother had not aborted or miscarried.

Skull x-ray films with tomograms of the sella turcica and the base demonstrated marked hypoplasia of the right orbit and optic canal (Fig. 3). The right frontal bone and the right side of the sphenoids were small, resulting in a deformed and small right anterior fossa. There was a lucent defect in the right frontal bone with nonsclerotic margins. Two bony defects were noted at the skull base (Figs. 4-7): one was a 1-cm oval defect in the center of the sphenoid bone. A soft tissue density protruded through this defect into the right nasopharynx. The other defect was in the cribriform plate with absence of the medial portions of the roofs of both orbits. Another soft tissue density projected through this bony defect also. An x-ray

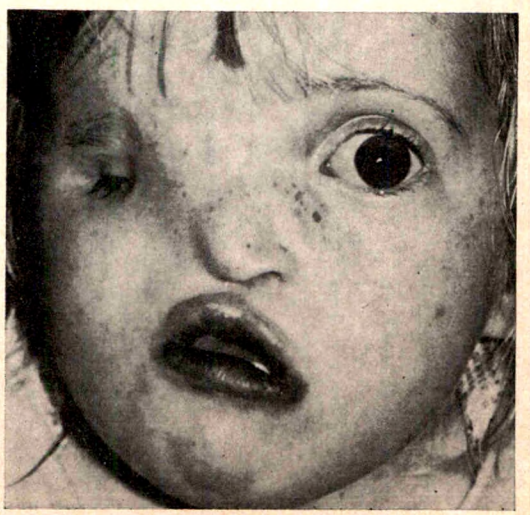


Fig. 1 (Goldhammer and Smith). Right cryptophthalmos, deformity of the nasal root.

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film of the cervical spine demonstrated a hemivertebra at C-7 and a deformity of the body of the vertebra C-4. The clavicles appeared intact.

Discussion

Failure of the eyelid fold formation, or ablepharia, is associated with either a well-formed eyeball, except for its anterior segment, or with microphthalmos. The skin of the forehead continues without interruption over to the skin of the cheek, and the eyeball becomes hidden in cryptophthalmos. It occasionally is impossible to differentiate without microscopic examination whether extreme microphthalmos or anophthalmia is present.[1] However, usually in cases of anophthalmia, the orbits and eyelids are barely affected.[1,2] Ida Mann[1] mentioned two causes of cryptophthalmos: (1) failure of the eyelid fold formation, and (2) subsequent destruction of the eyelids. In most cases, the cryptophthalmos is bilateral; partial conditions may also occur.

The absence of eyelashes was regarded as characteristic,[1,3] but they were present in several reports.[4-6] Thus, one would assume that the presence of eyelashes favors the etiology of secondary destruction rather than primary failure of the eyelid fold formation. Therefore, it is interesting that eyelashes occurred in familial cryptophthalmos cases. Our patient, however, who showed well-formed cilia, was sporadic.

Many other congenital anomalies are often associated with cryptophthalmos, and Fran-



Fig. 2 (Goldhammer and Smith). Total absence of the right external ear.

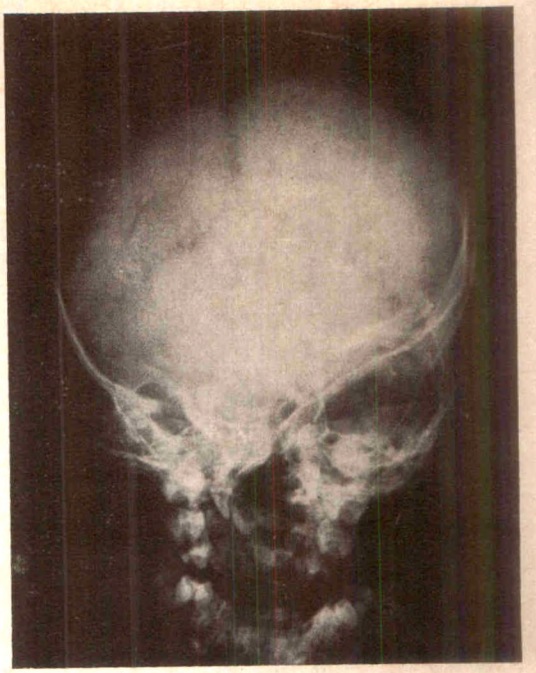


Fig. 3 (Goldhammer and Smith). Anteroposterior x-ray film of skull showing rudimentary right orbit, soft tissue mass in right nasal cavity.

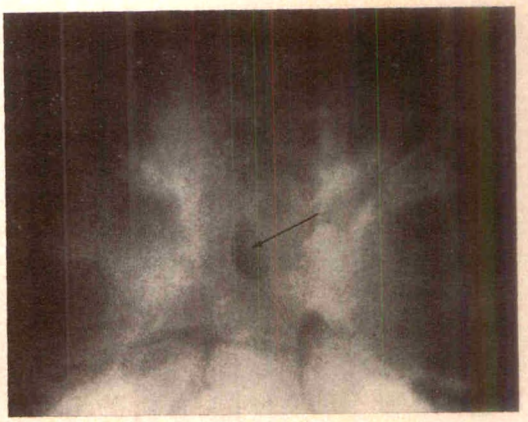


Fig. 4 (Goldhammer and Smith). Basal tomography demonstrating bony defect of the sphenoid body.

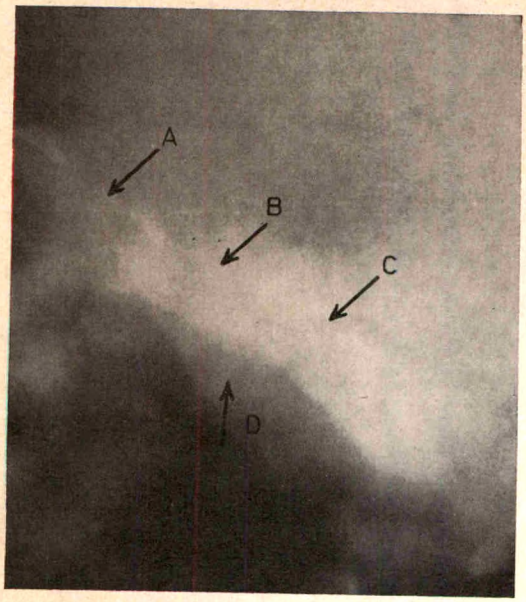


Fig. 5 (Goldhammer and Smith). Midsagittal tomography. A indicates bony defect of the ethmoid; B, bony defect of sphenoid body; C, normal sphenooccipital synchondrosis; and D, sphenopharyngeal encephalocele, indistinguishable from enlarged adenoids.

çois[7] grouped them into a syndrome with the following: (1) cryptophthalmos; (2) dyscephaly (meningoencephalocele, cleft lip and palate, and anomalies of the ear and nose); (3) syndactyly; and (4) genital anomalies. Our patient had marked cranial and facial anomalies, but no syndactyly or genital anomalies. On the other hand, she had multiple cardiac malformations. Further information about the etiology, heredity, pathology and associated anomalies can be found elsewhere.[8-12]

We are aware of only two reported cases of cryptophthalmos with meningoencephaloceles, and neither of these was the basal type. One was frontal[5] and the other parietal in location.[13] Duke-Elder[8] and others[6,9] refer to the first reported case of cryptophthalmos by Zehender[14] as having a meningoencephalocele. We studied his case carefully and could not find any evidence for this anomaly.

In our case, two basal encephaloceles were demonstrated. These are regarded as rare anomalies. However, basal encephalocele is probably often missed, as there is no prominent external mass, and it is infrequently noted on routine x-ray films. It should be suspected in any child with a median cleft syndrome, a flat broad nasal root, and hypertelorism. These characteristics are all present in the cryptophthalmos syndrome. The x-ray film diagnosis requires basal views of the skull, preferably with basal tomography. The fact that the diagnosis of basal encephalocele was not previously made in our case demonstrates how easily it can be overlooked. The

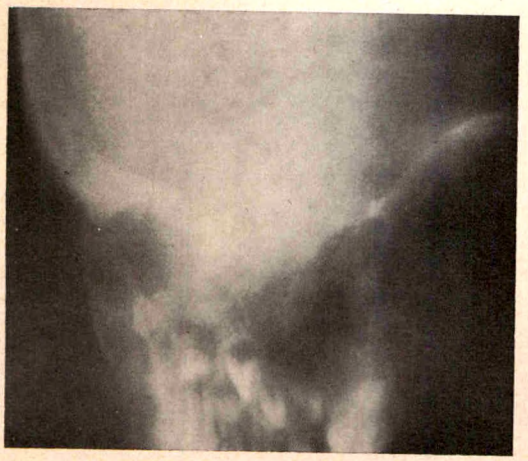


Fig. 6 (Goldhammer and Smith). Anteroposterior tomogram through the nasal cavity showing transethmoidal encephalocele. Note the asymmetric orbits.

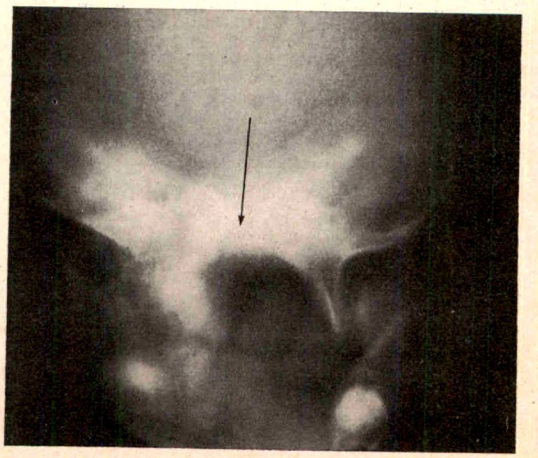


Fig. 7 (Goldhammer and Smith). Anteroposterior tomogram through the sphenoid body demonstrating the bony defect (arrow).

TABLE

OCULAR ANOMALIES ASSOCIATED WITH BASAL ENCEPHALOCELES

Hypertelorism
Exotropia
Microphthalmos
Cryptophthalmos
Peripapillary staphyloma
Optic disk anomalies
Pallor
Pits
Coloboma
Dysplasia
Megalopapilla
Bitemporal hemianopia

importance of recognizing the basal encephalocele lies in differentiating these soft tissue masses from tumors in the nose and nasopharynx. The dangers of such tumor biopsies are obvious. We previously discussed[15] ophthalmologic signs associated with basal encephalocele, with special reference to optic nerve anomalies. Cryptophthalmos must be added to the list of ocular anomalies associated with basal encephalocele (Table).

This case belongs to the cryptophthalmos syndrome, but it may also be related as an intermediary, in its auricular and vertebral defects, to the Goldenhar's oculoauriculovertebral syndrome.

SUMMARY

A 2,144-g white girl was born with absence of the right ear and eye, cleft lip and palate, two basal encephaloceles, tricuspid atresia, ventricular and atrial septal defects, detransposition of the great vessels, right aortic arch, and aberrant right subclavian artery. Through an oval defect in the center of the sphenoid bone, soft tissue protruded into the right nasopharynx. The medial portions of the roof of both orbits and the cribriform plate were absent and soft tissue protruded through this bony defect. Basal tomography was required to demonstrate the encephaloceles, which should be suspected in any child with a median cleft syndrome, a flat broad nasal root, and hypertelorism.

ACKNOWLEDGMENT

We thank Steven Weinstock, M.D., for referring the patient.

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NOTES, CASES, INSTRUMENTS

A CHIN-OPERATED SWITCH FOR MOTORIZED THREE-AXIS MICROSCOPIC MOVEMENT

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CHARLES MCCARTHY, AND
DANIEL EICHENBAUM, M.D.
Bethesda, Maryland

Motorized horizontal movement of the operating microscope recently became possible through the use of an X-Y coupling developed by Zeiss in conjunction with Machemer.[1] A unified foot switch to operate the X-Y functions, as well as focus (Z) and zoom, has also been constructed.[1]

In performing vitreous surgery, the surgeon holds the vitrectomy instrument in one hand and either traction sutures, the irrigated contact lens, or a second surgical device in the opposite hand. Frequent repositionings of the microscope are necessary because of high magnification (23X) and the small field of view. The use of a foot switch to operate the X-Y and Z functions of the microscope has resulted in several disadvantages. Foot positioning on the various foot switches is difficult without shifting, even slightly, body and hand positions. In addition, a foot switch[1] does not permit simultaneous movement of the microscope in two or three directions. Because repeated microscope realignment along the three principal axes is necessary during vitreous surgery, one foot must be used at all times to control microscope position. Only one foot, therefore, is free to operate all surgical modalities such as the vitrectomy instrument, intravitreal cautery, remote suction, and photography. This prohibits simultaneous operation of any two of these modalities.

We developed a chin-operated switch to control the X-Y-Z positioning motors of the operating microscope system. We chose the chin because of its ability to move independently in all three axes (up-down, left-right, and forward-backward) without head, eye, or hand movements. The device consists of six switches arranged along the three axes (X-Y-Z) connected to a joystick with a rubber padded disk on the end (Figure). The chin switch is actuated by consciously extending the chin to make contact with the switch and pushing the switch in the appropriate direction. Thus, inadvertent actua-

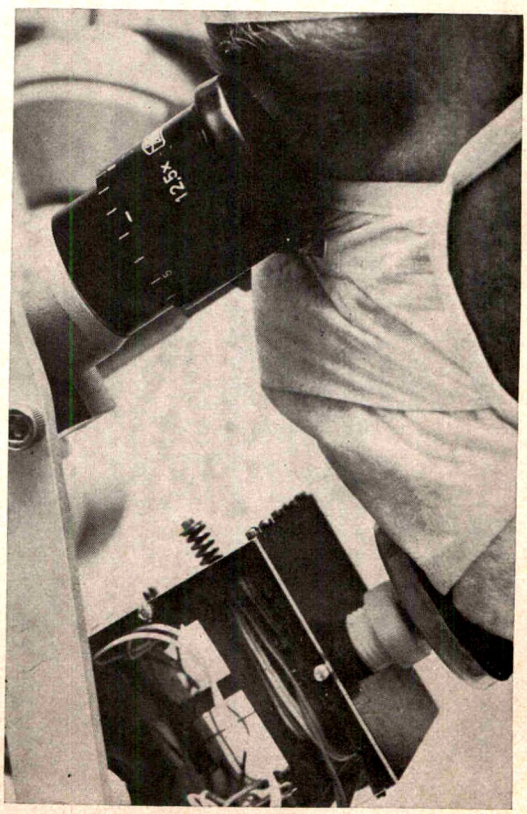


Figure (Charles, McCarthy, and Eichenbaum). The chin-operated switch is affixed to the operating microscope in apposition to the surgeon's chin.

From the Clinical Branch, National Eye Institute (Drs. Charles and Eichenbaum), and the Biomedical Engineering and Instrument Branch (Mr. McCarthy), National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Maryland.

Reprint requests to Steve Charles, M.D., Clinical Branch, National Eye Institute, National Institutes of Health, Bldg. 10, Rm. 10N313, 9000 Rockville Pike, Bethesda, MD 20014.

tion of the switch by talking or other head movement is eliminated. Because the amplitude of the chin movements necessary to actuate the switch is small, visualization through the microscope is never impaired. Firm extension of the chin actuates the motor to move the microscope away from the surgeon while less firm pressure moves the microscope toward the surgeon. Moving the switch pad to the left moves the microscope to the left and vice versa. Similarly, elevating the chin raises the microscope and chin depression lowers the microscope. Any of these motions may be used alone or in combination with others for simultaneous two- or three-axis movement. The position of the switch relative to the chin and the actuation pressures are adjustable to fit the surgeon's needs.

Summary

A chin-operated switch was developed to permit control of motorized operating microscope movement simultaneously along three axes. It permits use of both feet to operate surgical modalities, decreases microscope positioning time, and decreases needless hand movements.

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PROLONGED VERTICAL NYSTAGMUS AFTER PENTOBARBITAL SODIUM ADMINISTRATION

Simmons Lessell, M.D., Philip A. Wolf, M.D., and David Chronley, M.D.

Boston, Massachusetts

Up-beating, gaze-evoked vertical nystagmus is an important sign in neuro-ophthalmic diagnosis because it may indicate the presence of a lesion in the tegmentum of the pons.[1,2] This type of nystagmus can also occur in normal individuals who use barbiturates.[3] We examined several patients with gaze-evoked, up-beating vertical nystagmus who had no evidence of a brainstem lesion and who only used drugs—100 mg of pentobarbital sodium to promote sleep—12 to 48 hours before examination. The persistance of the nystagmus led us to inquire into the duration of the nystagmogenic effect of pentobarbital sodium.

Method

We studied 17 healthy, paid volunteers (ten women and seven men) between 20 and 30 years of age. Informed consent was obtained from the subjects for the investigations. They agreed to refrain from using alcohol and other drugs for the duration of the study. Immediately before and after 48 hours of abstinence from drugs, they were examined for the presence of nystagmus. None was found. Each subject then ingested 100 mg of pentobarbital. We examined them for nystagmus, 12, 36, 60, and 84 hours after drug ingestion. A subject had nystagmus if there were multiple beats of vertical nystagmus on gaze, with the fast component directed upward. Blood samples were obtained each time a subject had nystagmus. The blood was analyzed by gas liquid chromatography to detect the presence of chlordiazepoxide, diazepam, diphenylhydantoin sodium, glutethimide, methaqualone, meprobamate, methyprylon, and barbiturates. The subjects served as their own controls.

Six of the subjects had up-beating, gaze-evoked nystagmus 12 hours after ingesting a single dose of pentobarbital. Three of them had it at 36 hours, but none of the subjects had the nystagmus at 60 hours. Gas liquid chromatography did not detect the presence of any drug other than barbiturate in any of the subjects.

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Discussion

When oral barbiturates are prescribed, it is usually for sedation, hypnosis, or the prevention of seizures. These therapeutic effects are supposedly short in duration. Pentobarbital is most often used to promote and maintain sleep. An experimental investigation of hospitalized patients with chronic diseases (but with normal renal and hepatic function) showed that sleep lasts an average of 6.6 hours after a single oral dose of 100 mg of pentobarbital.[4] There are other effects, however, that may last longer. "Hangover" for example, may follow sleep induced by pentobarbital. Hangover could be the result of inhibition of the rapid eye movement phase of sleep by the drug, but it also could be a direct effect of the drug. Unmetabolized barbiturates can be detected in plasma for several days after a single intravenous dose of 50 mg of pentobarbital.[5] Other barbiturates may produce prolonged effects on the nervous system. In one study, psychologic testing showed that judgment and other intellectual functions were impaired for almost 22 hours after a single oral dose of 200 mg of secobarbital.[6] Our investigation supports the existence of prolonged effects of barbiturates on the nervous system. Vertical nystagmus might conceivably persist even longer than our subjects demonstrated, in patients who use larger doses of barbiturates, who use it chronically, who ingest other drugs concurrently, who ingest the barbiturate on a full stomach, or who have systemic diseases that impair detoxification.

Since up-beating, gaze-evoked vertical nystagmus may persist for at least 36 hours after a single hypnotic dose of pentobarbital, physicians should exercise caution in assessing the implication of this sign in patients who have ingested a barbiturate a few days before examination.

Summary

Of 17 healthy adults without nystagmus who ingested 100 mg of pentobarbital sodium, six had up-beating, gaze-evoked vertical nystagmus 12 hours later. Three of them had nystagmus 36 hours later, but none of them had it 60 hours later. Therefore, one should be reluctant to ascribe this type of nystagmus to a disease of the central nervous system in patients who received a barbiturate within several days of examination.

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CORNEAL FORCEPS

J. L. Bustillo, M.D.

Edmonton, Alberta

I believe microsurgical instruments, while miniaturized in the lower segment that enters the operative field, could be of larger, more comfortable proportions in the rest.

A pair of corneal forceps* (Figure) combines a large overall size—13.5 cm long, about the same as a ball-point pen, with 1.5-cm wide handles—with delicate long branches and

* Available from Storz Instrument Co., 3365 Tree Court Industrial Blvd., St. Louis, MO 63122.

Reprint requests to J. L. Bustillo, M.D., 630 Professional Bldg., Edmonton, Alberta, T5J 2B3 Canada.

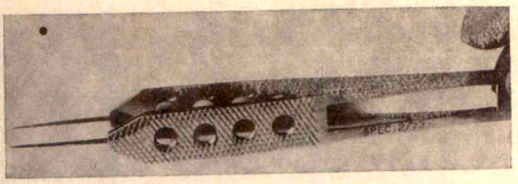


Figure (Bustillo). Corneal forceps.

0.15-cm teeth. The forceps are fenestrated for lightness and are finely corrugated for easy grip.

Summary

A pair of corneal forceps combining a large overall size with delicate features—13.5 cm long, 1.5-cm wide handles, and 0.15-cm teeth on the branches—is fenestrated and finely corrugated for easy grip.

RETROBULBAR HEMORRHAGE OCCURRING AFTER PLACEMENT OF A SUPERIOR RECTUS MUSCLE SUTURE

Irwin S. Weiss, M.D.

Los Angeles, California

Retrobulbar hemorrhage is usually due to a retrobulbar injection, severe trauma, or orbital injury.[1] It may also occur spontaneously in diseases affecting blood vessel wall integrity or blood clotting, such as scurvy, uremia, or hemophilia.[2] Although it is usually considered a benign condition, recent reports documented closure of the central retinal artery following retrobulbar hemorrhage.[3] In addition, rare occurrences of blindness following cosmetic blepharoplasty may be due to retrobulbar hemorrhage, the site of which is unclear.[4-6] A retrobulbar hemorrhage occurred after the placement of a superior rectus muscle traction suture.

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Case report

A 25-year-old white woman, followed for bilateral keratoconus, had visual acuity of R.E.: 20/400, and L.E.: 20/40 with a contact lens. There was no evidence of systemic disease. The patient underwent a full-thickness keratoplasty in the right eye under general anesthesia. There was no retrobulbar injection or other manipulation of the orbit. Immediately after placing a 4-0 silk superior rectus muscle suture, a large hematoma formed under the conjunctiva. The conjunctiva was incised and the hemorrhage appeared to subside. Several hours after uneventful surgery the patient complained of severe pain. The next day a retrobulbar hemorrhage was diagnosed (Figure). Intraocular pressure was 35 mm Hg and visual acuity was approximately 20/400. A small sector of iris was incarcerated in the wound. Platelet counts and bleeding and clotting times were normal. Postoperative treatment consisted of topical corticosteroids, cycloplegics, and orally administered acetazolamide (Diamox). No other problems developed and the graft remained generally clear. Six weeks after surgery the patient was lost to follow-up.

Discussion

Recent reports have emphasized the danger of retrobulbar hemorrhage. Retrobulbar injection and orbital exploration cause hemorrhage by direct injury to an artery or large vein, but how this occurs in cosmetic blepharoplasty is unknown. In the latter procedure, bleeding may occur during the mobilization of vascularized orbital fat or by inci-

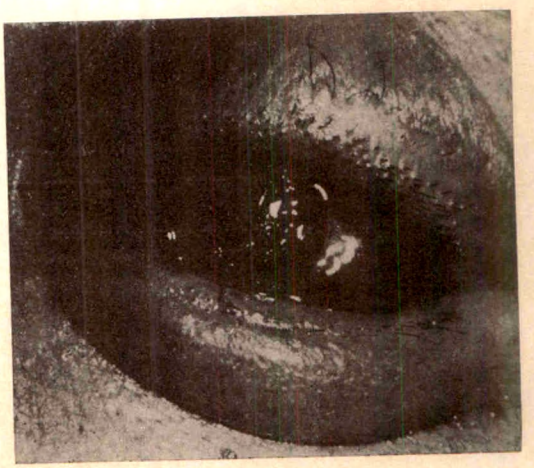


Figure (Weiss). Retrobulbar hemorrhage one day after surgery. The only orbital manipulation was insertion of a superior rectus muscle bridle suture.

dental injury to an extraocular muscle. Injury to a muscle could happen during the injection of local anesthetic beneath the septum, from scissors cuts used to open the septum, or in the act of grasping orbital fat. A needle injury to an extraocular muscle is capable of causing a retrobulbar hemorrhage, as amply demonstrated by this case.

Summary

A retrobulbar hemorrhage occurred in a 25-year-old woman after placement of a superior rectus muscle traction suture. In evaluating the causes of a retrobulbar hemorrhage, one must consider the possibility of a needle injury to an extraocular muscle.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY 1975 SPRING MEETING

The Association for Research in Vision and Ophthalmology's (ARVO) 1975 spring meeting opened Monday, April 28, 1975, in Sarasota, Florida. It was preceded by the informal meeting of many who arrived on Saturday and Sunday. Informal meetings on the beach by old and new researchers, both clinical and basic, were in the manner of a family reunion and were a highlight of the meeting. Members came from both the United States and abroad to present and hear the 587 scheduled papers. There were 1,364 registered participants. This alone represented a unique attendance, for among the ARVO membership of 2,100, 993 of those attending were members, the remainder being nonmember registrants.

The program format was unusual. Six different meetings were conducted simultaneously at five different hotels for five days from 9 to 12 and 4 to 7 o'clock. The enthusiastic participant, by careful planning, fast walking, and some luck in catching the ever-present two-tiered English buses going from hotel to hotel, was able to shuttle to the papers of interest. The subjects were far ranging and the advance program had to be studied with some attention to plan one's activities. Each scheduled paper had an abstract in the program with the precise time of presentation, for which a personal agenda preparation was imperative. For example, while Robert Weinberg was describing the importance of the serum lysozyme test in sarcoid uveitis on Monday at 10:15, Paul Ocken was discussing the relationship of histocompatability antigen to primary open-angle glaucoma which may point to the use of this antigen as a genetic marker. At the same time, Dwain Fuller was reporting the retinal damage that light from a fiber optics bundle could cause in the eye, and Wlod Kozak was giving his interpretation of the color sensations of subjects as they were presented colors at various brightnesses. Stuart Lipton was describing the in vivo studies of the role of cyclic nucleotides of a toad retina with uni-intracellular microelectrode recordings, while in yet another hotel, Durgan Bhuyan was explaining his analysis of the role of catalase in the regulation of hydrogen peroxide in the tissues of the eye. The discussion of each paper, all of which were presented in ten minutes with five minutes for discussion, brought up relevant points useful to an ophthalmologist.

Most of the research was new; hence, the fortunate clinician who attended these meetings was seeing vignettes of articles not scheduled for publication for two years or more. The program is designed in such a fashion that the abstracts of submitted papers are required only four months prior to the meeting. The research is thus truly fresh. That some of the new findings will not hold up to further scrutiny was apparent in some discussion periods. For the most part the papers were of sound quality and often presented by new clinical investigators as their first major lecture at a national meeting.

This year the late George Smelser, who had contributed greatly to ARVO, was honored with two superb symposia—the first on the anatomy and pathology of the eye, in which the ultrastructure of the cornea was stressed, and the second on corneal wound healing in which the histologic, physiologic, and biochemical aspects of the subject were discussed.

One half-day session was devoted to the "Physiological aspects of glaucoma." David Campbell and W. Morton Grant reported that the extreme plasticity of fresh red blood cells did not seriously hinder outflow, but when the red blood cells degenerate as

from an old vitreous hemorrhage, they become more spherical and rigid, fail to pass through the 5-μ Millipore opening, and cause marked resistance to outflow. A second half-day session was devoted to another aspect of glaucoma, "Axoplasmic transport and disk topography." From this session the observer left feeling almost confident that before long the geometry of the disk will be machine-readable, and the clinician may have one more valuable tool to assist in the assay of the progression of the glaucoma disease state. Other examples of special sessions included corticosteroids and glaucoma, biochemistry of cataracts, and stereoscopic vision.

Carl Kupfer, director of the National Eye Institute, gave a report on the President's budget for the next fiscal year. The outlook for even maintenance of the present level of support is bleak indeed. It was obvious that we members of the ophthalmic community should contact our senators and representatives directly if we are to avoid a catastrophic decline in ophthalmic research. The National Eye Institute has developed greatly, but the present cutback is certainly inappropriate, at least to this observer.

One of the other strengths of the meeting was the number of recognized experts who were in attendance when papers in their field of expertise were presented. Thus, well-founded critiques were given if justified, and ill-founded critiques were similarly appropriately discouraged. During the intermission from noon until 4 P.M., the beach provided the necessary format to query speakers further and for potential cooperative studies to be generated.

Thursday morning marked the awards lectures which were comprehensible to the clinician even though both were electrophysiological in nature. Dr. Tsumeo Tomita, in the Proctor Medal Lecture, gave a synopsis of his life's study of the electrical behavior of retinal cells. The Friedenwald Award was shared by David Hubel and Torsten Wiesel, who gave further insight into the function of individual cells in the primate visual cortex. The most dramatic portion of their presentation was that in which they were able to show, through axonal transport of labeled amino acids, that there was regular arrangement of the cortical cells appropriately related to their binocular arrangement. One millimeter of monkey visual cortex represents about 7 degrees of peripheral visual field and only a fraction of that of central field. A rule of thumb evolved: to get from one isolated retinal area to another separately distinguishable retinal point, one must go about 1 mm in the visual cortex, whether referring to the central or peripheral vision.

The Thursday morning meeting of the entire group was the only time in the five days in which no decision was necessary as to which paper one should try to hear. Such an intellectual smorgasbord of papers relating to the eye would seem to lead to indigestion and an avoidance of further fare, but that did not seem to be the case, for the last sessions on Friday afternoon were exceptionally well attended.

As the meeting closed the common objective of most was attendance at the meeting next year. No further testimony to the quality of the meeting would seem necessary. Those plans came from clinicians and researchers alike, for here had been presented something for everyone. Since the attendance has been growing at the rate of approximately 15% per year, the big question will be how to get in and out of the limited meeting rooms next year if growth continues. The group could move to larger quarters, but then who likes to leave home?

ROBERT D. REINECKE

III WORLD CONGRESS OF SOCIETY OF EYE SURGEONS

The III World Congress of the Society of Eye Surgeons of the International Eye Foundation was held April 15-17, 1975, in San Salvador, El Salvador, Central America, with Humberto Escapini, president of the Sociedad Salvadoreño Oftalmologia, as honorary president. Some 150 ophthalmologists from 30 nations registered together with their families. The program participants came from some 22 different countries, and from every continent but Australia. Our hosts were congenial, the scientific sessions lively, and an interesting meeting was had by all.

The Society of Eye Surgeons was organized in 1969 as the medical supporting arm of the International Eye Foundation. The International Eye Foundation began in 1961 as the International Eye Bank with the indefatigable J. Harry King, Jr., as its guiding spirit. It has provided fresh and preserved eye tissue for some 7,500 keratoplasties together with surgical teaching teams, teaching fellowships, paramedical training, and established eye surgery units in 13 different nations. The emphasis has been on training and developing the skills of individuals with regard to the circumstances and country in which they will work rather than providing facilities and equipment which may be unavailable to them when they return to their native lands.

The Derrick Vail Gold Medal was awarded to Professor Jules François, of Belgium, for his contributions to every phase of ophthalmology—as teacher, practitioner, executive, editor, investigator, and writer (Figure). Professor François paid beautiful tribute to the long-time editor of the American Journal of Ophthalmology, praising him for his generous heart, the goodness and nobility of his spirit, and his fertile imagination. Professor François provided a systematic survey of the various steps in cataract extraction and emphasized the number of steps that have been adopted as routine in recent years.

The Walter S. Atkinson Lecture was given by Frank W. Newell, of Chicago, who discussed a variety of topics dealing with general anesthesia.

The sessions opened with a number of leading national political figures of El Salvador present. Mr. Romulo O'Farrill, of Mexico City, and Mrs. William T. Spence, of Washington, D.C., received medals of honor from the Society for their long-time



Figure (Newell). Professor Jules François wearing the Derrick Vail Gold Medal.

contributions to the International Eye Foundation. This was followed by the Vail Lecture and by sessions on plastic and orbital surgery, extraocular muscles, and ophthalmology in emerging nations.

The following day there were sessions on glaucoma, diseases of the retina, and abnormalities of the anterior segment. The next day saw a long session on keratoplasty, another on cataract, and a concluding discussion, chaired by Richard C. Troutman, that covered a variety of surgical topics.

The hospitality of the organizing group was unusually warm and generous. The women of the El Salvador Society labored mightily at the black lava sand beach of El Zunzal preparing hot chiromal, huge oysters on the half shell, and the characteristic El Salvador pupusas—two tortillas filled with meat or cheese. All this preceded a spectacular buffet lunch and Indian dances. The drive along the coastal highway provided beautiful views of the Pacific Ocean with black beaches of lava sand. Another day, after the scientific session we toured the Izalco volcano. The Salvadorian Ophthalmological Society worked energetically to make this a successful meeting. Those who attended will long remember the hospitality of their Latin American friends.

The meeting concluded with a gala banquet, and a tired but enthusiastic group proceeded to Puerto Rico by jet, while others returned home.

The next meeting of the Society of Eye Surgeons will be in 1977 at a site to be designated. The International Eye Foundation will sponsor a Second World Congress on the Cornea April 28 to May 1, 1976. Information is available from the Foundation at the Sibley Hospital, Washington, D.C. 20016.

FRANK W. NEWELL

AMERICAN JOURNAL OF OPHTHALMOLOGY

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Published monthly by the Ophthalmic Publishing Company
233 East Ontario St., Chicago, Illinois 60611

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X PAN AMERICAN CONGRESS OF OPHTHALMOLOGY

The X Pan American Congress of Ophthalmology was held April 20-25, 1975, in the Caribe Hilton Hotel, San Juan, Puerto Rico. A. Edward Maumenee, president of the Pan American Association, and Guillermo Picó, president of the Congress presided. Some 975 ophthalmologists registered for the meeting together with some 700 family members as well as additional technical exhibitors. The full scientific program had courses in both Spanish and English and the meeting was a success clinically, scientifically, and socially.

The first Pan American Congress of Ophthalmology was held in Cleveland in 1940 but only some 20 Latin Americans attended. The second was held in Montevideo, Uruguay, in November 1945 but few North Americans were present. With this Congress the Pan American emerged as a leading international ophthalmic society of the Western Hemisphere.

The important educational function of the Pan American Association in uniting the family of American nations was emphasized by the formation of the Pan American Society of Microsurgery and the Pan American Glaucoma Society. These are in addition to the already established Pan American Pathology Society and the Pan American Strabismological Society. All of these groups met before the Congress and provided scientific programs in their special fields.

The program lent itself to superlatives with much new and exciting material presented. Dr. Maumenee arranged 15-minute lectures on current topics by ophthalmologists from every continent who described the latest work in their institutions. There were multiple programs with ophthalmic films including the Conrad Berens Film Festival, courses in both English and Spanish, and scientific programs in specialty areas. This led to presentation of some 70 different papers in the morning scientific sessions, some 40 films, and 219 scientific

papers in the afternoon sessions. Additionally, courses were provided in both Spanish and English in plastic surgery, microsurgery, lacrimal duct surgery, glaucoma surgery, and retinal detachment surgery.

As president of the Congress, Guillermo Picó of Puerto Rico arranged an outstanding, efficient, and impressive meeting. The sessions started promptly; scientific papers were presented with effective translations provided; projection facilities were good; and the organization of the program was a tribute to all those responsible.

The inaugural session was one of many welcoming speeches including those by the president of the Pan American Association, A. Edward Maumenee; the president of the Congress, Guillermo Picó; and the dynamic Benjamín Boyd, executive secretary of the Association who is responsible for the outstanding direction of the Association. The Catholic cardinal of Puerto Rico gave the invocation and we were welcomed by the governor of Puerto Rico. On the dais were Professor Jules François, president of the Internation Council of Ophthalmology, Sir John Wilson, president of the International Agency for the Prevention of Blindness, and university and medical officials.

Dr. Fernando de Boca, a special assistant to President Gerald Ford, provided a delightful speech in both English and Spanish that captivated his listeners. Citizens of the United States were proud of the warm, discerning representation of their country.

The Gradle Lecture was given by Raul Rodriguez of Uruguay who described a spectacular surgical procedure of scleral trabeculokeratoplasty. It was extremely well done and illustrated with a beautiful motion picture. Happily for everyone Mrs. Gradle attended and presented the traditional silver bowl.

Lorenz Zimmerman provided the III Pan American Lecture of the American Journal of Ophthalmology, "Ophthalmologic Manifestations of Granulocytic Sarcoma (Chloroma)." As is always true, Zimmerman's lecture provided a wealth of correlation between pathologic changes and clinical disease.

The social events were in the tradition of warm hospitality of the Pan American Association. After the official opening of the Congress, Sunday evening the group retired to the historic San Jerónimo Fort for the president's reception. They were greeted by the military trumpets and then entertained with music and folk dances. The spectacular fort provided a most memorable evening. A beach party filled another evening and on another a banquet and dancing followed a reception under a full moon in the gardens of the hotel. Spouses were entertained apace while the ophthalmologists attended to their duties at the scientific sessions.

Guillermo Picó received the Gradle medal, the highest award of the Association. The Pan American Gold medal of the International Society for the Prevention of Blindness went to A. Gerard DeVoe of New York City; Stuart Brown of Pittsburgh received the first award of the Conrad Berens Film Festival for his film, "The dry eye. Diagnosis and pathogenesis."

Guillermo Picó who has conducted the basic course in ophthalmology at the University of Puerto Rico for the past seven years made special awards on behalf of the university to those in the hemisphere responsible for the success of the course. This course has already provided 176 ophthalmologists with a six-month course in basic ophthalmology. Those receiving the awards included Mr. William O'Connor of the Alcon Laboratories, Benjamín Boyd, A. Gerard DeVoe, J. Harry King, and Carl Kupfer.

The executive committee selected Santiago, Chile, for their next meeting, the home of the new president of the Association, Juan Arentsen. The next meeting will be held February 20-25, 1977.

It was a tired but happy group that con-

cluded the meeting with a picnic on the grounds of the Bacardi Company. It was a very full week and there was unanimous agreement that the organizers of the Congress performed a miracle of efficient administration and hospitality.

FRANK W. NEWELL

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper; with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

NEOVASCULARIZATION AFTER LASER PHOTOCOAGULATION OF MACULAR LESIONS

Editor:

I wish to take issue with Professor François and his colleagues in regard to two points raised in their recent paper (François, J., DeLaey, J. J., Cambie, E., Hanssens, M., and Victoria-Troncoso, V.: Neovascularization after argon laser photocoagulation of macular lesions. Am. J. Ophthalmol. 79:206, 1975).

The first point of disagreement relates to the authors' statement that, "the close relationship between the treated area and the early appearance of neovascularization after treatment proves the relationship with photocoagulation." The de novo appearance of subretinal neovascularization or the growth of preexistent new vessels shortly after argon laser photocoagulation in various macular diseases is well known.[1-3] However, it can occur as a part of the natural course of these diseases, and studies in which patients have been observed with serial fluorescein angiograms have documented the growth of subretinal new vessels over relatively short periods of time in the absence of treatment.[4-7] Therefore, although the appearance of subretinal new vessels in the vicinity of the areas of laser treatment in the patients of François and associates shortly after photocoagulation is noteworthy, it does not prove a causal relationship. The experimental studies in which intense laser burns resulted in fibrovascular membranes arising from the choriocapillaris in rabbit eyes are of interest but do not strengthen the conclusions of this paper. The vasculature of the rabbit retina and its metabolism are sufficiently different from that of the human to invalidate comparison in this context.

A second point at issue deals with the indications for laser photocoagulation in the two patients who had disciform macular scars in one eye and angioid streaks in the fellow eye but excellent vision and no symptoms. In cases of angioid streaks with loss of macular function in one eye, the second eye may not decompensate for many years. Moreover, such patients initially become symptomatic due to subretinal fluid accumulation with serous detachment of the neurosensory retina before subretinal neovascularization and hemorrhage appear.[8] Since the efficacy and risks of photocoagulation are uncertain, such treatment should be withheld at least until sufficient clinical evidence of progression is present to indicate the imminence of visual loss. If one does plan to photocoagulate in diseases which produce macular subretinal neovascularization, I believe one should treat much more heavily than François and associates did.[1] This, however, remains only a "clinical impression." Whether photocoagulation of any variety or intensity is of value in macular diseases remains a moot question which cannot be decided by multiple case reports such as many of us have published, and to which the contribution of Professor François and his colleagues can be added. Rather, I believe that randomized, controlled clinical trials of photocoagulation in various macular disease entities should be initiated, along the lines of the nationwide Diabetic Retinopathy Study now in progress.

ROBERT N. FRANK, M.D.
Bethesda, Maryland

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Reply

Editor:

Dr. Frank discusses four points. The first relates to the appearance of subretinal neovascularization or the growth of preexistent new vessels after argon laser photocoagulation of various macular diseases. Dr. Frank agrees that the new vessel formation may be due to the photocoagulation. Conversely, we agree that it may occur as a part of the natural course and even in senile asymptomatic eyes in the absence of treatment.[1] We should, therefore, have written that the clinical appearance of the neovascularization suggests (and not proves) the relationship with photocoagulation. This relationship is nevertheless strongly suggested by the early appearance of the neovascularization in the treated area (six to eight weeks). Deutman suggested moreover that a direct trauma to Bruch's membrane and choroid may produce subretinal neovascularization (personal communication, 1974). This author saw a disciform lesion in an eye, which had been injured some weeks earlier by a copper wire. The lesion was similar to that of presumed histoplasmosis. Surprisingly a small copper filament was found in the vitreous. After perforating the sclera, the copper wire could have injured the macular region.

The second point of Dr. Frank's letter relates to the treatment of asymptomatic cases. Dr. Frank thinks that the treatment is contraindicated. That is exactly what our own experience seems to prove. On the other hand, Dr. Frank thinks that one must treat heavily, when photocoagulation seems to be indicated to eradicate an eventual subretinal neovascularization. The light intensity used in our cases was nevertheless relatively high (up to 300 mW).

The third point relates to our experiments in rabbits. Dr. Frank points out that the argon laser photocoagulation was of greater intensity than in human patients and that the anatomic or metabolic conditions are different in rabbits. This is of course true, but the neovascularization produced in these animals nevertheless demonstrates the potential danger of the treatment.

The fourth point relates to controlled studies and trials for the treatment of macular diseases. Dr. Frank[2] stated correctly, "It appears most reasonable to say that the criteria for photocoagulation in diseases causing macular subretinal neovascularization cannot be stated rigidly until there is more information about the effectiveness of such treatment. To settle this question will require a meticulously designed, large scale controlled study of photocoagulation in macular diseases." We agree that there is a need for controlled studies. They are, however, difficult and hazardous in the treatment of macular diseases, just as they are in diabetic retinopathy, because neither two eyes nor two cases are exactly the same and because the natural course differs from one case to another. Therefore the conclusions will be largely dependent on personal experiences and subjective observations.

There is an agreement between Dr. Frank's and our conclusions. The only real disagree-

nent consists in one word—"proven" instead of "suggested."

The purpose of our paper was mainly to stress the potential danger of argon laser photocoagulation in macular diseases with diseased Bruch's membrane, and the importance of a careful follow-up of the treated cases. That a subretinal neovascularization can be induced or aggravated by the treatment seems to us and other authors, really possible. Moreover, Dr. Frank[2] agrees that the rapid growth or de novo appearance of subretinal neovascularization after laser photocoagulation suggests a relationship.

PROFESSOR JULES FRANÇOIS
Ghent, Belgium

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BOOK REVIEWS

THE INTRAOCULAR IMPLANT LENS: DEVELOPMENT AND RESULTS, WITH SPECIAL REFERENCE TO THE BINKHORST LENS. By M. E. Nordlohne. The Netherlands, Dr. W. Junk N.V., Publishers, 1975. Paperbound, 269 pages, table of contents, 91 black and white figures, 4 color plates. $30.94

This new book is timely particularly since its publication in January 1975 coincides with a rebirth of interest in intraocular lens implantation. Indeed, there are now probably more implants being used in California in a month than in Holland in a year, and such sweeping claims for their safety and efficacy are being made that certainly every ophthalmologist removing cataracts must consider using this technique.

The author begins with the quotation from Theodore, "Aphakia is the first complication of cataract extraction," and cites the various data supporting his thesis that the intraocular lens is the best optical means of restoring vision after cataract extraction. In Chapter 2, he describes the development of these lenses to the presently advocated iridocapsular lens of C. D. Binkhorst and establishes Binkhorst's role as a leader in this field. Chapter 3, on techniques, describes the management of complications, some unique to the implantation of an intraocular lens, such as endothelial corneal dystrophy. It becomes evident that often the worst thing to do in the face of a complication is to remove the implant. Rather it is proposed that the eye be treated around the offending foreign body. Chapters 4 through 7 deal with results—first, those of Binkhorst and his co-worker Worst, then those of the author, and finally those of 26 Dutch ophthalmologists "inspired by Binkhorst's example to start fitting lens implants themselves." On page 197 is the italicized statement, "Binkhorst and others with him, however, have always wondered whether Binkhorst lens implants operations can suitably be performed by any given ophthalmologist." This, of course, is the crux of the question. Any operation to be useful universally should indeed be transferable with minimal additional risk to any qualified ophthalmic surgeon. Conventional extracapsular extraction, as recommended by Binkhorst for implantation of his iridocapsular lens, is easily performed by a qualified cataract surgeon. However, only five ophthalmologists, 19.2% of the participating Dutch ophthalmologists, believe that every ophthalmologist should be able to perform a Binkhorst lens implant. The author states that "lens implantation should not form part of the course of ophthalmological training at this moment."

Two short final chapters deal with histopathology, intraocular pressure, position of the lens within the eye in relation to position of the patient, and the subjective visual impression of the patient wearing such a lens or lenses.

I found the statement on page 121 most

interesting, "Until Jan. 1, 1972, Binkhorst inserted 170 iridocapsular lenses in 158 patients. The first operation took place on Sept. 16, 1965." Again, on page 138, "The most remarkable advantages of the iridocapsular implant seem to be the marked decline in the incidence of endothelial corneal dystrophy, decentration, and macular damage." An average interval of three years after operation till the detection of endothelial corneal dystrophy, as observed in iris clip lens implantations, was reached only by 8.8% of the iridocapsular lens cases as opposed to 64% of the iris clip lens cases. . . . It is therefore hoped that endothelial corneal dystrophy will remain absent (in these cases)." Nordlohne states finally, "Only time will tell if this expectation is justified." On the basis of the data presented in this text, I believe it is certainly unjustified to use intraocular lenses after intracapsular extraction or by secondary implantation. Except for the first 170 eyes reported by Binkhorst, the majority of iridocapsular implant cases have less than three years' follow-up, certainly insufficient time to judge their eventual rate of complication.

Nordlohne is to be congratulated on his objective and thorough presentation of this controversial subject.

RICHARD C. TROUTMAN

LECTURE NOTES ON OPHTHALMOLOGY, 5th edition. By Patrick D. Trevor-Roper. Philadelphia, J. B. Lippincott Co., 1975. Paperback, 123 pages, table of contents, 75 black and white figures and 14 color plates. $7.25

This fifth edition of Lecture Notes on Ophthalmology maintains its initial goal of providing ophthalmologic information to the "harrassed final year students" of a medical curriculum that generally is finding less, instead of more, space for ophthalmology. There has been some revision of the text, reorganization of the chapters, but, as the author notes, "the overall pattern remains fairly constant, and this little book struggles to contain its middle-aged spread."

The text is arranged in a problem format, especially helpful for students who are presented with discussion about the painful red eye, gradual loss of sight in quiet eyes, sudden loss of sight in quiet eyes, an injured eye, and the like.

It is pocket-size and fits nicely in a lab coat. There are 14 color plates, which could be used to somewhat better advantage. The photographs and color drawings are placed together. It would be helpful to have more text surrounding these prints, and more care should be given to the educational appropriateness of those that are included. Others could be substituted with greater educational impact. Several of the illustrations are, indeed, excellent, such as the outline of repair of retinal detachment.

The inclusion of a brief section on tropical ophthalmology provides information not generally available in American texts.

The presentation is concise and yet contains considerable depth in some areas beyond what might be expected in a student text (particularly with the discussion of surgical techniques and diagrams). It may be of help to nonophthalmic surgeons who may wish greater information for College of Surgeons examinations and the like. It is an attractive book that could be further enhanced by improved illustrations, both black-and-white and color, and could significantly benefit from a more problem-solving approach for the student in the diagnostic steps necessary to reach a final diagnosis of the problems outlined.

BRUCE SPIVEY

CATARACT AND ABNORMALITIES OF THE LENS. Edited by John G. Bellows. New York, Grune and Stratton, Inc., 1975. Cloth-bound, 533 pages, table of contents, index, over 100 black and white figures. $36.50

Since cataract is the disease most fre-

quently seen by ophthalmologists, it must come as a surprise to many that few all-inclusive books dealing solely with the crystalline lens have been published during the past 40 years. The pace of technological growth, the information explosion of the basic sciences in ophthalmology, and the sophistication of surgery of the lens have made monographs on the subject nearly extinct. Bellows's Cataract and Anomalies of the Lens was published in 1944. Bellows has again involved himself with a treatise on the lens, but this time as an editor with 46 other contributors.

The book is divided into 15 topics, which fall into three main subdivisions. The first deals with laboratory science and includes subjects such as molecular embryology, classical embryology, fine structure, biochemistry, holography, echography, and pathology. This comprises 191 pages. The second subdivision spans 166 pages and involves a complete description of cataracts of various etiologies. Highlighted are developmental, toxic, nutritional and metabolic, traumatic, dislocated, endocrine, and senescent cataracts. The final portion of the book comprises 140 pages and is devoted to cataract surgery and its complications.

Bellows has selected expert contributors and organized their efforts in a step-by-step treatise on the lens. The inevitable variation in literary style and manner of presentation does not detract from the end result.

It is impossible to analyze critically every chapter. The reader soon realizes that the basic science subjects do not exist in a vacuum in some remote laboratory but emerge as a sound basis for a clinical approach to disorders of the lens. Greguss notes that the rate of cataract development can be documented by making holograms from the lens at fixed intervals so that the formation of light scattering centers can be well followed. Coleman emphasizes that the cataractous lens no longer appears as a sonolucent area within the lens capsule but contains inhomogeneities of the lens interior which can be seen ultrasonically. Ultrasonic biometry lends itself ideally to the study of the translational movements of the lens during accommodation and after the instillation of drugs. The visual evaluation of the eye with opaque media is of enormous practical importance. Yanoff's presentation of the pathology of cataract is both complete and scholarly. The section on cataract types is handled with great precision.

I found some weaknesses in the final section in that the views expressed appeared at times too one-sided.

NORMAN S. JAFFE

SYMPOSIA

ATTI DEL VI CONVEGNO. Edited by Professor Luigi Cardia. Bari, Italy, Societa Oftalmologica Meridionale, 1973. Paperbound, 397 pages, index, over 250 black and white figures. $32

SYMPOSIUM ON OCULAR THERAPEUTICS

B. STRAMPELLI: **Surgical therapy on cosmetic defects following destruction of the globe**

G. MORONE AND U. MANFREDINI: **Treatment of bulbous keratopathy**

M. MAIONE AND M. MANGILI: **Treatment of keratoconjunctivitis sicca**

R. FREZZOTTI: **Treatment of herpes simplex keratitis**

M. BONNET: **Use of photocoagulation in the treatment of chorioretinitis**

C. B. BIETTI AND C. BISANTIS: **Treatment of diabetic retinopathy**

G. AURICCHIO: **Medical treatment of glaucoma**

P. L. PAUFIQUE: **Trabeculotomy**

R. CARAMAZZA: **Results of primary intervention with trabeculotomy**

F. REDI V. DE MOLFETTA: **Observation on the use of trabeculotomy ab externo**

B. SCUDERI, G. URSO, E. BALESTRAZZI: **Goniotomy in the treatment of congential glaucoma**

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M. D'ESPOSITO, G. SANNA: **Utilization and value of the electroretinogram in the diagnosis and treatment of neuro-ophthalmological disorders**

C. BALACCO-GABRIELI, M. R. BRACCIOLINI, G. SEORGIA: **Passage of large spectrum antibiotics into the anterior chamber**

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

ALBRECHT VON GRAEFES ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE OPHTHALMOLOGIE

ELECTRON MICROSCOPIC STUDIES ON ZONULAR FIBERS. Takei, Y., and Smelser, G. K. (Dept. Ophthalmol., College Physicians and Surgeons, Columbia Univ., New York, N.Y.). Albrecht von Graefes Arch. Klin. Ophthalmol. 194:153, 1975.

Adult rabbit zonular fibers were treated with collagenase, α-chymotrypsin and hyaluronidase. The results of the action of these enzymes was observed with the electron microscope. Collagenase digests lens capsule but not zonular fibers. On the other hand, α-chymotrypsin digests zonular fibers and zonular lamellae but not the lens capsule. Hyaluronidase had little effect on either the lens capsule or the zonular fibers. Vitreous fibers were digested by collagenase but not by α-chymotrypsin or hyaluronidase. The authors conclude that zonular fibers closely resemble the microfibrils of elastic fibers. (12 figures, 45 references)—David Shoch

TREATMENT OF EALES' DISEASE WITH PHOTOCOAGULATION. Spitznas, M., Meyer-Schwickerath, G., and Stephan, B. (Univ. Eye Hosp., Essen, Germany). Albrecht von Graefes Arch. Klin. Ophthalmol. 194:193, 1975.

The entire surface neovascularizations and microaneurysms were coagulated in 224 eyes with Eales' disease. Care was taken not to coagulate the widened and tortuous feeding-vessels since this is dangerous and may lead to a rupture of the congested vessels. Vessel proliferations extending into the vitreous cavity were occluded by coagulation of the base of their arterial and venous roots. No more than half of the retinal circumference was coagulated in one session. The patients have been followed for from 1 to 12 years with an average of five years. Of the 224 eyes, in 201 the disease was brought to a morphologic standstill. Visual acuity remained unchanged or improved in 185 of the eyes (87%). Post-coagulative macular puckering occurred in six eyes (3%). (4 figures, 4 references)—David Shoch

SCREENING TONOMETRY BY TECHNICIANS. Krieglstein, G. K. (Univ. Eye Hosp., Würzburg, West Germany). Albrecht von Graefes Arch. Klin. Ophthalmol. 194:221, 1975.

Comparative measurements of intraocular pressure of 200 eyes were statistical analyzed. Goldmann applanation tonometry was performed by the author and was accepted as a reference system for the measurements made by a technician using the Pneumatonograph, the GlaucoTest screening tonometer, the Halberg tonometer and the Schiötz tonometer. The technician was trained in the use of these instruments for two days. The Pneumatonograph results on seated patients were in good agreement with the Goldmann readings. The GlaucoTest screening tonometer to be a good screening instrument for ocular hypertensives and required only a short period of training for the technician. The Halberg tonometer did not give precise readings of intraocular pressure and was more difficult for technicians to use. The Schiötz tonometer appeared to be of limited value in screening tonometry since there was variation in the readings of body position and the agreement with applanation tonometry was not high. The major contribution of the study was to demonstrate that technicians could be made comfortable and confident of their findings with a variety of instruments. (5 figures, 1 table, 14 references)—David Shoch

FLUORESCEIN IN THE HUMAN OPTIC DISK. Goldmann, H. (Univ. Eye Clinic, Bern, Switzerland). Albrecht von Graefes Arch. Klin. Ophthalmol. 194:243, 1975.

Transfer of fluorescein through the vessels of the nerve head and into the nerve head were studied. Fluorescein diffuses into the disk tissue mostly from the surrounding tissues (uvea and sclera). Compressing the globe to intraocular pressures higher than the systolic ophthalmic artery pressure does not totally empty the capillaries of the disk. After intravenous fluorescein injection the plasma

layer at the wall of the retinal and papillary vessels is the source of vessel fluorescence. Therefore small vessels fluoresce almost as much as big ones and extravasates appear as very brilliant patches. Increasing the pressure in the eye diminishes the circulation in the disk vessels even more than in the retinal vessels. (5 figures, 2 tables, 2 references)—David Shoch

THE DIAGNOSIS OF PSEUDOTUMORS OF THE MACULA BY ULTRASONOGRAPHY. (German) Freyler, H. (Univ. Eye Clinic, Vienna, Austria). Albrecht von Graefes Arch. Klin. Ophthalmol. 194:283, 1975.

The echograms of 35 patients form the basis of this study. The chief difference between pseudotumors and malignant melanomas is the fact that the echogram of pseudotumors is characterized by extraordinary irregularity. If the tumor is over 1.5 mm in height, then the diagnosis can be made with certainty. If it is over 1.1 mm in height then there is a high degree of probability of differentiating it from a malignant melanoma. (1 figure, 1 table, 5 references)—David Shoch

ANESTHESIOLOGY

INTRAOCULAR PRESSURES IN CHILDREN DURING ISOFLURANE AND HALOTHANE ANESTHESIA. Ausinsch, B., Graves, S. A., Munson, E. S., and Levy, N. S. (Univ. of Florida College Med., Gainesville, Florida). Anesthesiology 42:167, 1975.

The effects of isoflurane and halothane on intraocular pressure were studied in 28 children. It is concluded that the intraocular pressures during anesthesia with these agents did not differ significantly from those in the sedated, cooperative, healthy pediatric patients. (4 tables, 11 references)—Joel G. Sacks

ARCHIVES OF NEUROLOGY

TRANSIENT ISCHEMIC ATTACKS DUE TO ATHEROSCLEROSIS. Toole, J. F., Janeway, R., Choi, K., Cordell, R., Davis, C., Johnston, F., and Miller, H. S. (Dept. Neurol., Bowman Gray School Med., Winston-Salem, N.C.). Arch. Neurol. 32:5, 1975.

Patients with transient ischemic attacks (TIAs) due to atherosclerosis were studied by aortocranial arteriography. Onset of TIAs was before age 55 in 24% and between 55 and 64 in 47%. Men exceeded women by two to one. Of 160 patients, 77 were treated medically and 82 surgically. Five died in the immediate postoperative period. In the survivors, mortality has been the same in the medically and surgically managed groups. For patients with multiple lesions, surgical reconstruction of the carotid arteries was associated with very high surgical risk. In the medically treated group, anticoagulant therapy reduced the frequency of TIAs, but did not appear to protect patients from stroke. Mortality was 23% at four years, 57% of deaths being attributable to myocardial infarction and 38% to stroke. (2 figures, 15 tables, 35 references)—Authors' abstract

REGIONAL CURARE TEST IN EVALUATION OF OCULAR MYASTHENIA. Horowitz, S. H., Genkins, G., Kornfeld, P., and Papatestas, A. E. (Mt. Sinai Hosp., New York, New York). Arch. Neurol. 32:84, 1975.

In seven of 14 patients with clinically restricted ocular myasthenia gravis, the regional curare test showed latent peripheral involvement. The test consisted of the intravenous administration of 0.2 mg d-tubocurarine into an ischemic arm followed by repetitive supramaximal percutaneous electrical stimulation of the median or ulnar nerves. This produced a decrease in the amplitude of the initial evoked potential and a decrement of greater than 10% in the amplitude of the succeeding three to five potentials at rates of 3, 5, or 15 stimuli/sec. Three patients underwent transcervical thymectomy with subsequent improvement in both electrical and clinical findings. Evaluation of all patients with ocular myasthenia gravis should include regional curare testing of clinically uninvolved peripheral nerves. Thymectomy should be considered for patients with abnormal results. (2 figures, 2 tables, 17 references)—Authors' abstract

CONTRALATERAL GAZE DEVIATION WITH SUPRATENTORIAL HEMORRHAGE. Keane, J. R. (Dept. Neurol., Univ. Southern California Med. Ctr., Los Angeles, Calif.). Arch. Neurol. 32:119, 1975.

Three patients with spontaneous supratentorial intracerebral hemorrhage had contra-

lateral sustained conjugate gaze deviation. The autopsies disclosed large thalamic-basal ganglia hemorrhages whose caudal extension was limited to the midbrain. Current knowledge of oculomotor localization does not adequately explain this "wrong-side" gaze deviation, and the mechanism remains obscure. The present cases suggest that thalamic hemorrhage can produce contralateral gaze deviation without involving postdecussation horizontal oculomotor pathways. Contralateral gaze deviation is not a rare occurrence with deep supratentorial hemorrhages, and awareness of this confusing sign should assist in localizing intracerebral hematomas. (5 figures, 21 references) —Author's abstract

OCULAR SKEW DEVIATION. Keane, J. R. (Dept. Neurol., Univ. Southern California Med. Ctr., Los Angeles, Calif.). Arch. Neurol. 32:185, 1975.

In 100 patients with ocular skew deviation, the lesion was usually on the side of the lower eye, particularly when patients with internuclear ophthalmoplegia were excluded, but exceptions were sufficiently frequent to diminish the clinical lateralizing value of skew. Pontine damage was most commonly encountered, but mid-brain-pretectal and medullary lesions were frequent. The onset of skew frequently coincided with acute brain stem damage, and while a wide variety of diseases produced skew deviation, stem strokes were present in more than two-thirds of the patients.

The hypothesis that skew results from damage to tonic otolith-ocular pathways is generally compatible with both the known anatomy of otolith pathways and the clinical presentation of skew. Otolith function testing in patients with skew, further anatomical definition of otolith-ocular pathways, and clinicopathological study of discrete lesions associated with skew should help resolve the causative role of the otolith organs in skew deviation. (3 figures, 3 tables, 37 references)—Author's abstract

ARCHIVES OF OPHTHALMOLOGY

APHAKIC RETINAL DETACHMENT; MANAGEMENT OF THE FELLOW EYE. Benson, W. E., Grand, M. G., and Okun, E. (Dept. Ophthal., Washington Univ. School Med., St. Louis, Mo.). Arch. Ophthalmol. 93: 245, 1975.

One hundred eighty-five patients with unilateral aphakic retinal detachment were studied to determine the frequency of retinal detachment in the fellow eyes undergoing cataract surgery. It was found to be four times higher than the frequency in those eyes that remained phakic (26% vs. 7%). Despite the high incidence of detachment, 94% of the aphakic group had a final visual acuity of 20/60 or better in the second eye. At the time of surgery, the macula was still attached in only 17% of the 185 first eyes as compared to 57% of the 21 second eyes that developed an aphakic retinal detachment. (3 tables, 9 references)—Authors' abstract

EXPERIMENTAL EYE RESEARCH

MEMBRANE WATER PERMEABILITY IN NORMAL AND CATARACTOUS HUMAN LENSES. Maraini, G., and Orsoni, J. G. (Univ. Eye Clinic, Parma, Italy). Exp. Eye Res., 20:121, 1975.

The permeability of lens membranes to water has been studied in human cataractous lenses and in transparent post-mortem lenses. Both the exchange of radioactive water and the flow of water under an osmotic pressure gradient have been measured. The experimental evidence obtained suggests that the osmotic behavior of a lens with early senile cataract approximates that of a perfect osmometer and that no significant difference exists between normal and cataractous lenses in the percentage of exchangeable water.

When the in vitro uptake of NA^{22} by cataractous lenses is investigated the results indicate a progressive deterioration of the mechanisms maintaining the impermeability of lens membranes to sodium. (6 figures, 19 references) Authors' abstract

IMPROVED CORNEAL STORAGE: PENETRATING KERATOPLASTIES IN RABBITS. Bigar, F., McCarey, B. E., and Kaufman, H. E. (Dept. Ophthalmol., College Med., Univ. Florida, Gainesville, Fla.). Exp. Eye Res. 20:219, 1975.

In the present study, rabbit corneas were stored in McCarey-Kaufman corneal bathing media (M-K media) at 4°C for up to 14 days and used as donor material in penetrating keratoplasties. These results were compared to penetrating keratoplasties with corneas

stored in refrigerated moist chambers. Evaluation of the graft clarity shows that all the M-K media stored corneas were clear from the day of surgery. This contrasted with the 14-day moist chamber stored grafts which were hazy for the first week then either became opaque or remained hazy. Electron microscopy of postoperative grafts of 14-day M-K stored donor corneas, show the endothelial ultra-structure to be normal by the third day postoperative. (1 figure, 1 table, 6 references) —Authors' abstract

Klinische Monatsblätter für Augenheilkunde

THE ELECTRICAL ACTIVITY OF RETINAL GANGLION CELLS IN RELATIONSHIP TO BLOOD PRESSURE. (German) Hoyer, J. (Instit. Physiology, Univ. Vienna, Austria). Klin. Monatsbl. Augenheilkd. 166: 185, 1975.

The author recorded single fiber activity in the optic nerve as an objective method for investigation of the function of the retina. This was done in cats and it was found that there was normal retinal function even in the presence of considerable variations in systemic blood pressure. The retinal function was normal with average common carotid pressures from 60 to 140 mm Hg. (4 figures, 9 references)—David Shoch

ALTERATIONS IN THE FUNDUS RESEMBLING FLECKED RETINA IN ONCHOCERIASIS. (German) Trojan, H. (Univ. Lome, Togo, Africa). Klin. Monatsbl. Augenheilkd. 166:220, 1975.

Onchocerciasis is a very widespread disease in Africa and frequently causes blindness. The author studied 50 patients and found that there were alterations in the retina similar to those described for the "flecked retina." Fluorescein angiography showed that these alterations are localized in the pigment epithelium of the retina and they are interpreted as being the result of an antigen-antibody reaction in the uveal tract. The reaction is apparently due to liberated endotoxins of dead microfilaria since the retinal changes appear after treatment of the onchoceriasis. (5 figures, 4 references)—David Shoch

Lancet

HL-A AND IDIOPATHIC OPTIC NEURITIS. Platz, P., Ryder, L. P., Nielsen, L. S., Svejgaard, A., Thomsen, M., and Wolheim, M. S. (Univ. Hosp., Copenhagen, Denmark). Lancet 1:520, 1975.

Fifty-four patients with optic neuritis were HL-A (SD) and LD typed. The typing did not seem to offer prognostic value regarding the later development of multiple sclerosis, although the observation period was short. (1 table, 5 references)—Joel G. Sacks

TREATMENT OF ACUTE HEMORRHAGE OF PITUITARY TUMORS. Zervas, N. T., and Mendelson, G. (Dept. Neurosurgery, Harvard Med. School, Boston, Mass.). Lancet 1:604, 1975.

Sudden headache, visual loss, and mental change developed in three patients with unsuspected pituitary tumors. In each case stereotaxic transnasal cannulation of the intrasellar mass demonstrated a liquid hematoma under moderate pressure which could be easily aspirated. Restoration of vision and relief from neurological disturbances was prompt. Radiation therapy was then administered to prevent recurrence. (3 references)—Authors' abstract

Laryngoscope

SPONTANEOUS AND POSITIONAL NYSTAGMUS: A REASSESSMENT OF CLINICAL SIGNIFICANCE. Dayal, V. S., Tarantino, L., Farkashidy, J., and Paradisgarten, A. (Univ. Toronto, Toronto). Laryngoscope 84:2033, 1974.

All types of nystagmus are encountered in peripheral and central lesions. By itself the type of vestibular nystagmus (except vertical spontaneous seen in this series in only central lesions) is not diagnostic of any lesion. It should be considered with other findings. Based on these findings, the discontinuation of the term benign paroxysmal nystagmus is suggested.

In a small number of cases retested over a year, a change from spontaneous to positional to paroxysmal positional nystagmus is shown. These changes are considered to reflect the

degrees of vestibular compensation that occur over a period of time. (5 tables, 35 references) —Authors' abstract

NEUROLOGY

DOWNBEAT NYSTAGMUS AS A SIGN OF BRAINSTEM INVOLVEMENT IN ACUTE MENINGOENCEPHALITIS. Shimizu, N., Weinberger, J., and Yahr, M. D. (Dept. Neurol., Mt. Sinai School Med., New York, N.Y.). Neurology 25:267, 1975.

Two cases of acute meningoencephalitis, presumably viral in origin, with brainstem involvement are reported. Common to both patients during the course of their illness was coma, downbeat nystagmus, and ataxia. Although both reached what appeared to be a terminal state, recovery began following treatment with corticosteroids. (2 figures, 20 references)—Authors' abstract

EDROPHONIUM INFRARED OPTOKINETIC NYSTAGMOGRAPHY IN THE DIAGNOSIS OF MYASTHENIA GRAVIS. Spector, R. H., Daroff, R. B., and Birkett, J. E. (V.A. Hosp., Neurol. Service, Miami, Fla.). Neurology 25:317, 1975.

Horizontal optokinetic nystagmus was measured by an infrared eye movement recording technique before and after the administration of intravenous edrophonium chloride in 16 patients with proved myasthenia gravis. All the patients, even those without clinically apparent ophthalmoparesis, demonstrated an increased amplitude of optokinetic nystagmus after administration of the drug. None of 12 control patients, many with ophthalmoparesis, showed increased optokinetic nystagmographic amplitude. The superiority of infrared recording techniques to electro-oculography was discussed. Edrophonium infrared optokinetic nystagmography proved to be a sensitive and specific test of myasthenic weakness in extraocular muscles. (1 figure, 4 tables, 11 references)—Authors' abstract

RADIOLOGY

POLYTOMOENCEPHALOGRAPHY OF THE OPTIC CHIASM AND ADJACENT STRUCTURES. Johnson, J. C., Lubow, M., and Stears, J. (Ohio State Univ. Hosp., Columbus, Ohio). Radiology 114:629, 1975.

The addition of polytomography considerably increases the sensitivity of pneumoencephalography. The chiasmatic area lends itself particularly well to investigation by polytomoencephalography. In a series of 28 patients, the transverse dimension of the optic chiasm ranged from 4 to 20 mm, with a mean of 18 mm. The posterior portion of the chiasm tended to be U-shaped; its anterior portion's shape was that of a dumbbell. Intra-chiasmatic tumors distort and enlarge the chiasm. The diaphragma sella is also particularly well evaluated by this technique. The study is safe, reliable, and can be repeated as needed. (8 figures, 18 references)—Authors' abstract

SCIENCE

TRANSMISSIBLE MINK ENCEPHALOPATHY: INFECTIVITY OF CORNEAL EPITHELIUM. Marsh, R. F., and Hanson, R. P. (Dept. Vet. Science, Univ. Wisconsin, Madison, Wis.). Science 187:656, 1975.

Corneal epithelium from hamsters dying of transmissible mink encephalography contained a virus titer of $10^{4.8}$ times the 50% lethal dose ($10^{4.8}LD_{50}$) per 0.05 milliliter when assayed as a cell suspension derived directly from the infected animal. After one passage in tissue culture, an equivalent concentration of cells contained only $10^{0.8}LD_{50}$ per 0.05 milliliter. It is concluded that corneal tissues are infectious; the infectivity may be mainly associated with free nerve endings. However, the most important immediate inference is that corneas from human beings affected with Creutzfeldt-Jakob disease are likely to be lethal if transplanted to healthy recipients. (1 table, 11 references)—Authors' abstract

TRANSACTIONS OF THE AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

THE SIGNIFICANCE OF THE ^{32}P UPTAKE TEST IN THE DIAGNOSIS OF POSTERIOR UVEAL MELANOMAS. Shields, J. A., Hagler, W. S., Federman, J. L., Jarrett, W. H., III, and Carmichael, P. L. (Wills Eye Hosp.,

Philadelphia, Pa.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:297, 1975.

One hundred consecutive histologically confirmed malignant melanomas of the posterior uvea on which the ^{32}P test was performed prior to enucleation, were classified according to cell type. The ^{32}P uptake results of the pure spindle cell melanomas were compared with the results in the mixed and epithelioid cell tumors. There appears to be no relationship between ^{32}P uptake and cell type using the Callender classification. The ^{32}P uptake results in the 100 melanomas were then compared with the results in the 30 benign lesions which are known to simulate melanoma occasionally. There was a significant difference in ^{32}P uptake between the benign and malignant lesions, and no false-positive results were encountered. (10 figures, 24 references)—Authors' abstract

THE NATURAL HISTORY OF MALIGNANT MELANOMA OF THE CHOROID: SMALL VS LARGE TUMORS. Davidorf, F. H., and Lang, J. R. (Dept. Ophthalmol., Ohio State Univ., Columbus, Ohio). Trans. Am. Acad. Ophthalmol. Otolaryngol. 79: 310, 1975.

Survival studies were done on a large group of patients who had had an enucleation for malignant melanoma. These melanomas were divided into those that were larger than 10 mm in diameter and 3 mm in height and those that were less than these figures. As might be expected, the mortality rate at the end of five years and at the end of ten years was higher for those patients who had had large tumors at the time of enucleation. The exact figures for the five year follow-up are that on the small tumor group 94% were alive at the end of five years and on the large tumor group only 64% were alive. At the end of ten years, 23% of the small tumor group had died of metastases while 46% of the large tumor group had died of metastases. Surprisingly, mixed and epithelioid tumors did not seem to have a worse prognosis than spindle cell tumors. Cell type may be of less prognostic significance than tumor size in the case of small melanomas. (1 figure, 7 tables, 12 references)—David Shoch

TRABECULECTOMY: A REEVALUATION AFTER THREE YEARS AND A COMPARISON WITH SCHEIE'S PROCEDURE. Spaeth, G. L., Joseph, N. H., and Fernandes, E. (Wills Eye Hosp., Philadelphia, Pa.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 79: 349, 1975.

Forty-nine patients requiring surgery for open-angle glaucoma were divided into two groups. On 27 patients the Scheie procedure was performed while on 22 a trabeculectomy was done. At the end of three years, the average intraocular pressure was 4 mm lower in the group that had a Scheie procedure than in the group that had had trabeculectomy. Further, the success rate is defined by achievement of the surgeon's objectives was higher in the group with the Scheie procedure. The long-term visual result was the same in the two groups. (7 tables, 14 references)—David Shoch

UNIOCULAR MIOTIC THERAPY. Levene, R. Z. (Univ. Alabama, Birmingham, Ala.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:376, 1975.

The beneficial and harmful effects of 2% pilocarpine and 0.125% echothiophate iodide were evaluated on the prospective study of uniocular miotic therapy using the fellow eye as a control. Thirty primary open-angle glaucoma patients were treated with pilocarpine alone over a median time of 55 months. Twenty-nine similar patients were treated initially with echothiophate iodide and subsequently with pilocarpine over a median time of 54 months. Pilocarpine is cataractogenic but the changes are less marked and require more time than those induced by echothiophate iodide. In the combined group of 118 eyes of 59 patients there were 11 optic disk changes and six glaucomatous field defects. There was no difference in incidence between the treated and control eyes. The results suggest that one should be conservative in prescribing miotics, including pilocarpine alone, for patients suspected of having glaucoma. (6 tables, 6 references)—Authors' abstract

VISION RESEARCH

ON THE MECHANISMS OF THE INTEROCULAR LIGHT ADAPTATION EFFECT. Paris, J., and Prestrude, A. M. (Dept. Psychol., Virginia Polytechnic Instit., Blacksburg, Va.). Vision Res. 15:595, 1975.

Lansford and Baker recently demonstrated that the adaptation state of the contralateral eye effects the sensitivity of the test eye during dark adaptation. Specifically, a smaller and dimmer contralateral preadapting field which partially overlaps the preadapting field seen by the test eye accelerates subsequent monocular dark adaptation. The present study replicated the interocular light adaptation (Lansford-Baker) effect and produced the same effect under different test conditions. By the use of limited wavelength contralateral preadapting fields it demonstrated the interocular light adaptation effect in both cone and rod segments of the dark adaptation curve and that the rod effect is larger. Both long and short wavelength contralateral preadapting fields enhanced the effect to the point of doubling its magnitude. (11 figures, 1 table, 26 references)—Authors' abstract

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received at least three months prior to the date of occurrence.

EYE FOUNDATION OF AMERICA: GLAUCOMA SYMPOSIUM

The Eye Foundation of America will sponsor a symposium on glaucoma, Feb. 13 and 14, 1976, in New Orleans. For further information, write George M. Haik, M.D., 1542 Tulane Ave., New Orleans, LA 70112.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY: ATLANTIC SECTION MEETING

The 1975 fall meeting of the Atlantic Section of the Association for Research in Vision and Ophthalmology will be held at the Duke University Eye Center, Durham, North Carolina, Nov. 14-15, 1975. In addition to the presentation of papers on ophthalmic research, a symposium will be held on retinitis pigmentosa. Residents and ophthalmologists are invited to submit papers for presentation at this meeting. The registration fee is $2.00 per person; $10.00 with dinner. For further information, write Maurice B. Landers III, M.D., Program Director, Box 3802, Duke University Eye Center, Durham, NC 27710.

NEW JERSEY ACADEMY OF OPHTHALMOLOGY AND OTOLARNYGOLOGY: ANNUAL FALL MEETING

The Annual Fall Meeting of the New Jersey Academy of Ophthalmology and Otolaryngology will be held Nov. 12, 1975, at the Robert Treat Hotel in Newark, New Jersey. The morning session will be devoted to a cataract symposium and a corneal symposium will be given in the afternoon. For further information, write Marshall S. Klein, Executive Secretary, Eye Institute of New Jersey, 15 S. 9th St., Newark, NJ 07107.

ESTELLE DOHENY EYE FOUNDATION: ANNUAL POSTGRADUATE CONFERENCE

The Estelle Doheny Eye Foundation will present its Annual Post-graduate Conference Oct. 23 and 24, 1975, at the Health Sciences campus of the University of Southern California, Los Angeles. Guest speakers will include Douglas Anderson, Richard Brubaker, Bernard Schwartz, John Hetherington, Ralph Levene, Paul Lichter, and Kenneth Richardson. The Estelle Doheny and the A. Ray and Wendell C. Irvine Memorial Lectures will be delivered by Robert Shaffer and W. Morton Grant. For further information, write the Conference Chairman, Estelle Doheny Eye Foundation, 1355 San Pablo St., Los Angeles, CA 90033.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY: PACIFIC SECTION MEETING

The Pacific Section Meeting of the Association for Research in Vision and Ophthalmology will be held Sept. 18 and 19, 1975, at the University of Oregon School of Medicine, Portland, Oregon. For further information, write Lynette Feeney, Ph.D., Department of Ophthalmology, University of Oregon School of Medicine, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201.

NATIONAL ADVISORY EYE COUNCIL ANNOUNCES NEW MEMBERS

R. W. Lamont-Havers, acting director of the National Institutes of Health, announced the appointment of four new members to the National Advisory Eye Council, a consultative body to the National Eye Institute. The four new members are: Jay M. Enoch, John E. Harris, A. Edward Maumenee, and Mrs. Tommie M. Young. As members of the Council they will advise the National Eye Institute on the awarding of grants for research related to disorders of the eye and visual system, and provide guidance on program planning and development and research policy.

PREVENTION OF BLINDNESS SOCIETY: POSTDOCTORAL RESEARCH FELLOWSHIP

The National Society for the Prevention of Blindness announces a postdoctoral research fellowship program designed to provide financial support for physicians with outstanding research potential for training in basic biomedical sciences related to an understanding of the eye and its diseases. Each award is in the amount of $8,000 per year with a $500 annual increment and $500 for each dependent. An annual expense allowance of $1,000 is given to the recipient's laboratory. Fellowships are normally for a period of three years.

Because of the limited funds available, the Society will not make more than one award in any one year for training in a given laboratory.

Any physician who is planning a career in ophthalmic research related to the purpose of the Society is eligible to file an application. Applications from established scientists or advanced fellows or from individuals over 40 years of age will not be accepted.

Application forms and further information may be obtained by writing to the Committee on Basic and Clinical Research, National Society for the Prevention of Blindness, Inc., 79 Madison Ave., New York, NY 10016.

National Institutes of Health Unit Renamed

The National Institute of Neurological Diseases and Stroke has been renamed the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

Children's Eye Care Foundation: Research Fund

The Children's Eye Care Foundation of Washington, D.C., announces the establishment of a research fund to encourage research in pediatric ophthalmology. Limited grants are available to physicians who propose to undertake or who are currently carrying out a research activity in the field of pediatric ophthalmology. Proposals for grants up to $1,000 will be accepted until Dec. 31, 1975. Address proposals to Thomas D. France, M.D., Children's Eye Care Foundation, c/o Department of Ophthalmology, University Hospitals, Madison, WI 53706.

National Society for the Prevention of Blindness: Glaucoma Symposium

The National Society for the Prevention of Blindness will present a Glaucoma Symposium, Sunday, Sept. 21, 1975, in the ballroom foyer of the Sheraton-Dallas Hotel. The chairman is Paul R. Lichter. The panel members included Bernard Becker, John Hetherington, Jr., Allan E. Kolker, A. Edward Maumenee, Robert N. Shaffer, and Richard J. Simmons. There is no charge.

Personals

Endre A. Balazs

Endre A. Balazs has been appointed professor of ophthalmology and director of the Research Division of the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, to succeed the late George K. Smelser. Dr. Balazs is currently research director of the Department of Connective Tissue Research, Boston Biomedical Research Institute, lecturer at Harvard Medical School, and visiting professor in the Department of Chemistry, Salford University, Salford, England.

Peter Y. Evans

Peter Y. Evans has been named chairman of the Department of Ophthalmology at Georgetown University School of Medicine, Washington, D.C. Dr. Evans has been acting chairman since July 1973.

Kenneth L. Roper

Kenneth L. Roper, received the Alumni Merit Award of the Creighton University School of Medicine at the annual merit awards banquet in the Brandeis Student Center in Omaha, Nebraska, April 5, 1975.

David Worthen

Fifty of the 850 physicians and allied health personnel who are members of the American Medical Joggers Association ran in the Boston Marathon April 21, 1975. David Worthen, M.D., professor and chairman of the Department of Ophthalmology at the University of California, San Diego, led the medical group in 2:35:23. He has posted the best time for medics five years in a row.

FIVE-YEAR OPHTHALMIC MEETING CALENDAR

For listings, write Bruce E. Spivey, M.D., Professor and Chairman, Pacific Medical Center, Department of Ophthalmology, P.O. Box 7999, San Francisco, CA 94120.

1975

AUGUST	3-6	17th Congress of the Colombian Ophthalmological Society	Bogota, Colombia
SEPTEMBER	21-25	American Academy of Ophthalmology and Otolaryngology	Dallas
OCTOBER	5-11	World Medical Association Annual Meeting	Tokyo
	13-17	American College of Surgeons, Clinical Congress	San Francisco
	19-22	American Board of Ophthalmology (oral)	Philadelphia
	19-24	Tenth Congreso Argentino de Oftalmologia	Buenos Aires
NOVEMBER	2-6	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
	12-15	International Symposium on Cataracts	Iowa City
	29-DEC. 4	American Medical Association, Clinical Convention	Honolulu

1976

JANUARY	6-15	Dedication, new facilities, Bascom Palmer Eye Institute	Miami
	17	American Board of Ophthalmology (written)	Multiple sites
		Ophthalmic Knowledge Assessment Program, AAOO (written)	Multiple sites
APRIL	5-9	European Congress of Ophthalmology	Hamburg, Germany
	28-May 1	II World Congress on the Cornea	Washington, D.C.
MAY	7-10	American Board of Ophthalmology (oral)	Philadelphia
	14-16	American Ophthalmological Society	Kilauea, Hawaii
	16-21	Pacific Coast Oto-Ophthalmological Society	Seattle
JUNE	13-19	Club Jules Gonin Meeting	Lausanne, Switzerland
	26-JULY 1	American Medical Association, Annual Convention	Dallas
AUGUST	8-13	Asia Pacific Academy of Ophthalmology	Denpasar, Bali, Indonesia
SEPTEMBER	12-16	American Academy of Ophthalmology and Otolaryngology	Las Vegas (tentative)
OCTOBER	11-15	American College of Surgeons, Clinical Congress	Chicago
	21-24	American Board of Ophthalmology	San Francisco
NOVEMBER	11-15	Association of American Medical Colleges	San Francisco
DECEMBER	2-5	American Board of Ophthalmology (oral)	Chicago
	4-8	American Medical Association Clinical Convention	Philadelphia

1977

FEBRUARY	20-25	XI Pan American Congress of Ophthalmology	Santiago, Chile
APRIL	24-28	Pacific Coast Oto-Ophthalmological Society	Tucson, Arizona
MAY	4-7	American Board of Ophthalmology (oral)	San Francisco
	15-20	Instituto Barraquer VII International Course	Barcelona
	30-JUNE 1	American Ophthalmological Society	Hot Springs, Virginia
JUNE	18-23	American Medical Association Annual Convention	San Francisco
OCTOBER	16-19	American Board of Ophthalmology (oral)	Philadelphia
	17-21	American College of Surgeons Clinical Congress	Dallas
NOVEMBER	6-10	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
DECEMBER	4-7	American Medical Association, Interim Convention	Chicago

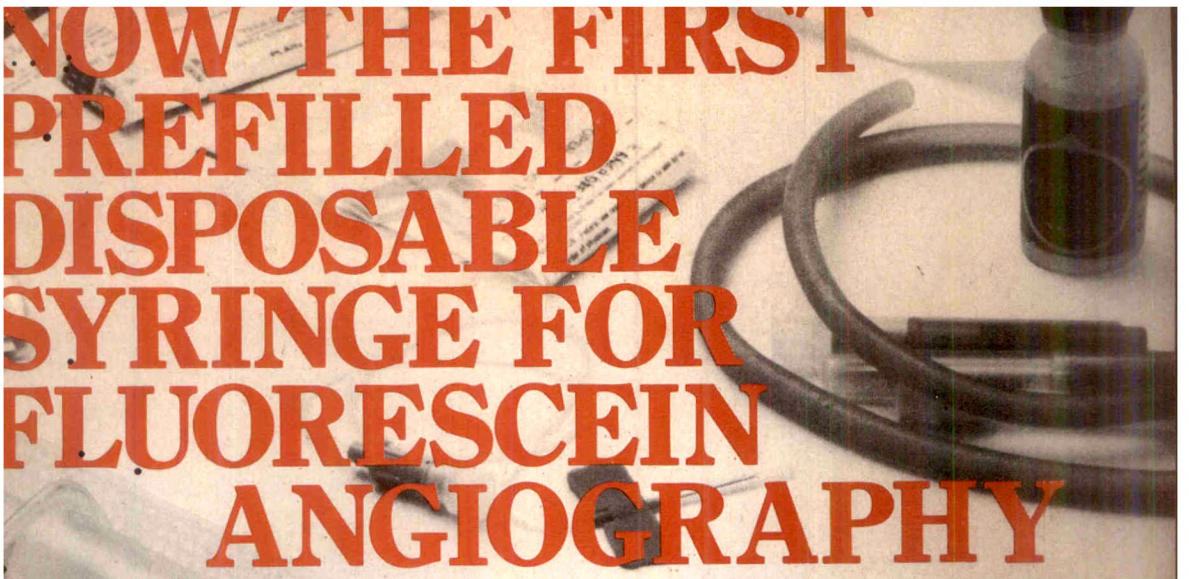
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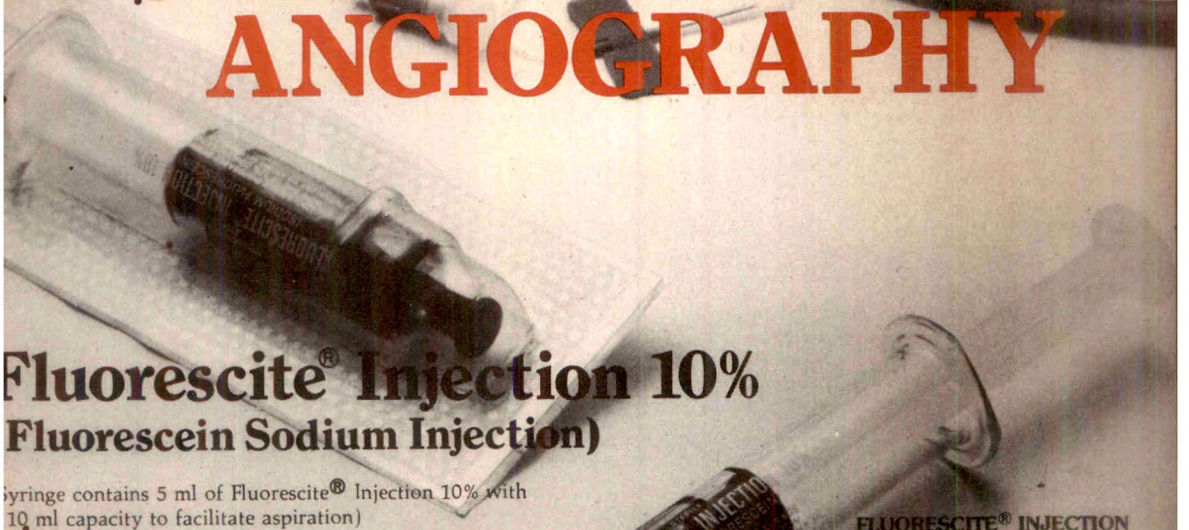
MAY	14-21	International Congress of Ophthalmology—Concilium Ophthalmologicum Universale	Kyoto, Japan
	29-31	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	16-20	American College of Surgeons Clinical Congress	San Francisco
NOVEMBER (tentative)	5-9	Association of American Medical Colleges	New Orleans

1979

MAY	28-30	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	22-26	American College of Surgeons Clinical Congress	Chicago
NOVEMBER	4-8	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.

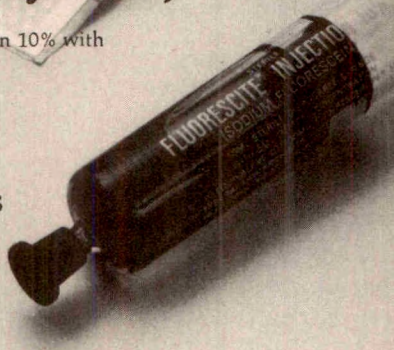
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CONTRAINDICATIONS High vitreous pressure and a gaping incisional wound, congenital cataracts, and patients under 20 years because of probable lens-vitreous adhesion not responsive to alpha-chymotrypsin lysis.

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ADVERSE REACTIONS Transient increases in intra-ocular pressure, moderate uveitis, corneal edema and striation have been reported. Delayed healing of incisions have been reported but has not been confirmed.

DOSAGE AND ADMINISTRATION Using aseptic technique transfer 5 ml. of the ALPHA CHYMAR® DILUENT to the vial containing ALPHA CHYMAR®. The resulting solution contains 150 N.F. Units per ml. which is equivalent to a 1:5000 dilution of alpha-chymotrypsin. The balance of the ALPHA CHYMAR® DILUENT may be used to flush out the enzyme solution after the zonules are digested.

NOTE: After the operation discard unused portion, including the diluent.

CAUTION: Excessive heat may alter alpha-chymotrypsin—do not autoclave the powder or reconstituted solution. Do not use if the reconstituted solution is cloudy or contains a precipitate.

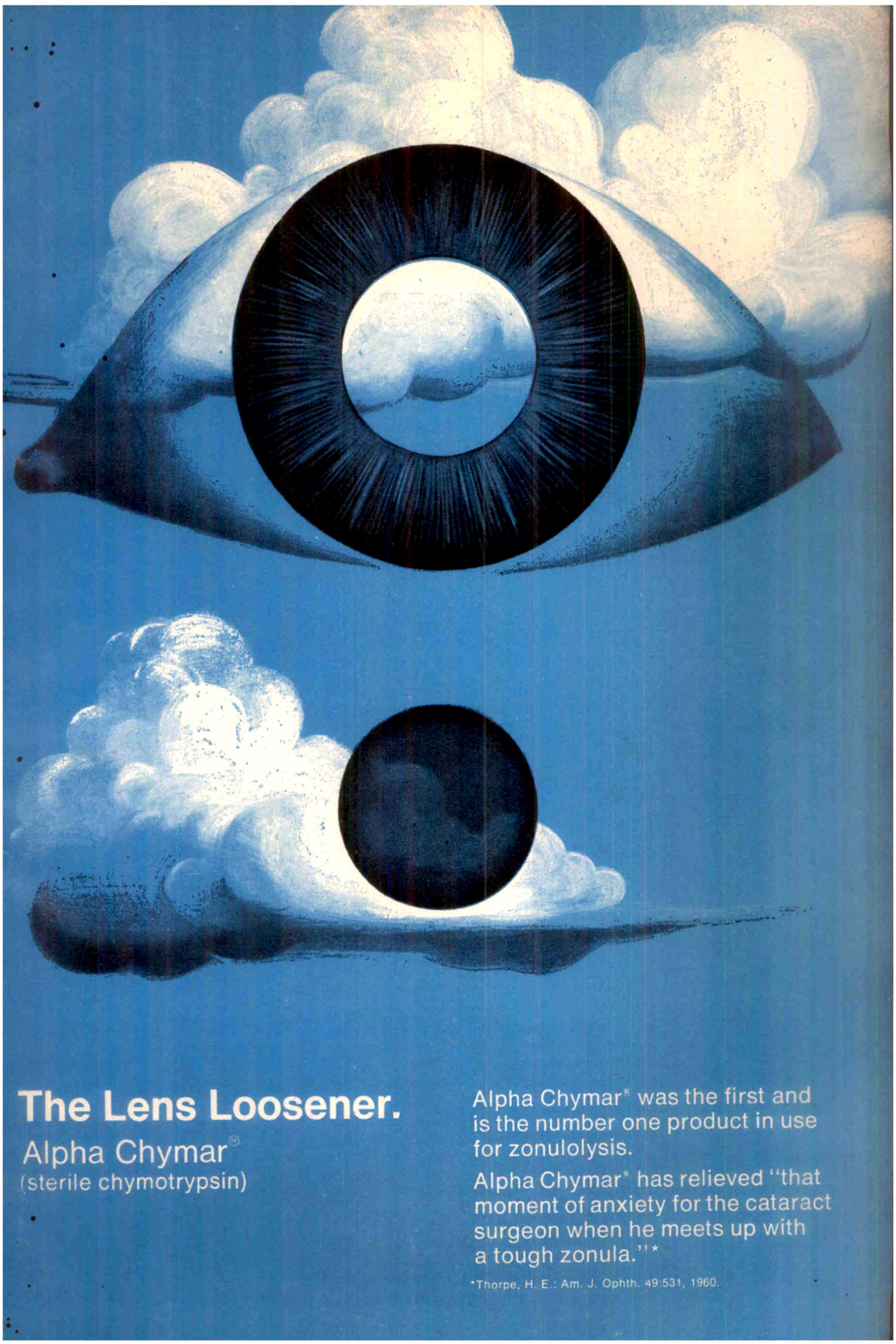
SUGGESTED PROCEDURE

(1) Dilate pupils with a suitable mydriatic.
(2) Either local or general anesthesia may be used.
(3) Make corneoscleral or corneoscleral-conjunctival incision.
(4) Irrigate the posterior chamber (under the iris) with about 1-2 ml. of ALPHA CHYMAR® (Sterile Chymotrypsin) solution.
(5) Perform peripheral or complete iridectomy or iridotomy.
(6) Place sutures if not preplaced. (Chromic or silk recommended).
(7) Wait two to four minutes then irrigate with at least 2 ml. of the unused portion of the Diluent, or Sodium Chloride Injection, U.S.P.
NOTE: If the zonules are still intact, irrigate with an additional 1-2 ml. of ALPHA CHYMAR® solution. This irrigation may be made through the iridectomy opening. After two to four minutes, irrigate with about 2 ml. of Diluent or Sodium Chloride Injection U.S.P. and attempt lens delivery.
(8) Extract with erisophake or forceps—tumbling delivery may be used if desired. Forceps should be used with caution to avoid possible dislocation of the lens posteriorly.
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18th Annual Meeting
American Society of Ocularists

Saturday Before A.A.O.O.
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Registration 8:00-9:00 A.M.

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Royal Coach Motor Hotel
3800 West Northwest Hwy.
Dallas, Texas

The scope of the 1975 American Society of Ocularists Meeting will integrate basic and fundamental definitions, concepts and techniques with the clinical management of the anophthalmic patient.

8:00 a.m. Registration and Coffee

9:00 a.m. *NEW & BASIC DEFINITIONS / CONCEPTS / TECHNIQUES*
This section is designed to define specific terminology, develop current concepts and detail specific techniques for the ocularist and ophthalmic surgeon.
John Kelley / Paul Gavaris, M.D. / William Cox / Dan Barr, M.D.

10:30 a.m. *ANOPHTHALMIC PATIENT MANAGEMENT—PANEL A*
This section will emphasize the ocularist's and ophthalmologist's approach to specific case presentations with discussion from the floor.
Robert Thomas / Charles Leone, M.D. / Phillip Danz / Robert Schimek, M.D.

12:00 LUNCHEON AND SCIENTIFIC EXHIBITS

1:15 p.m. A. S. O. LECTURESHIP

1:45 p.m. *ANOPHTHALMIC PATIENT MANAGEMENT—PANEL B*
This section will emphasize the ocularist's and ophthalmologist's approach to specific case presentations with discussion from the floor.
Robert Scott / Allen Putterman, M.D. / Orville Sankey / James Hargiss, M.D.

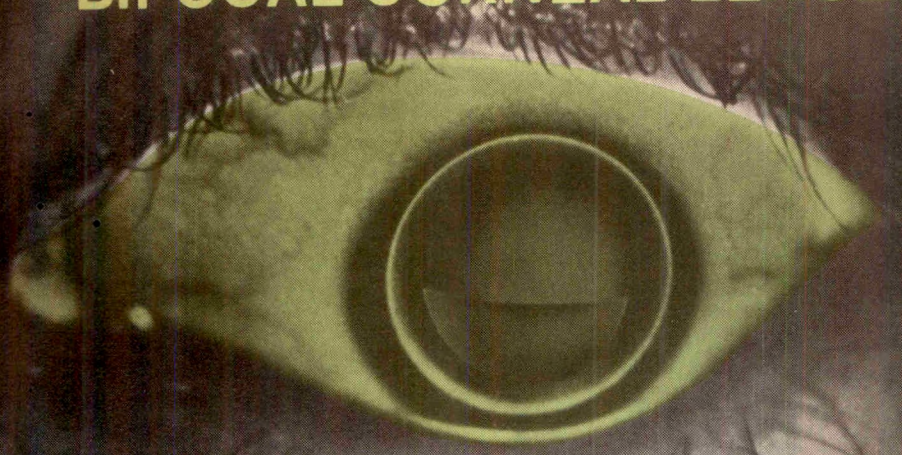
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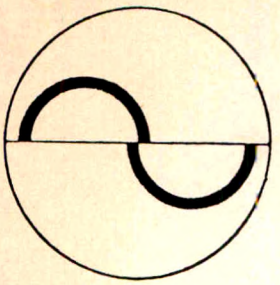
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The National Society for the Prevention of Blindness will present a Glaucoma Symposium, Sunday, September 21, 1975 in the ballroom foyer of the Sheraton-Dallas Hotel, Dallas, at 2:00 p.m. The chairman is Paul R. Lichter. The panel members include Bernard Becker, John Hetherington, Jr., Allan E. Kolker, A. Edward Maumenee, Robert N. Shaffer, and Richard J. Simmons. There is no charge.

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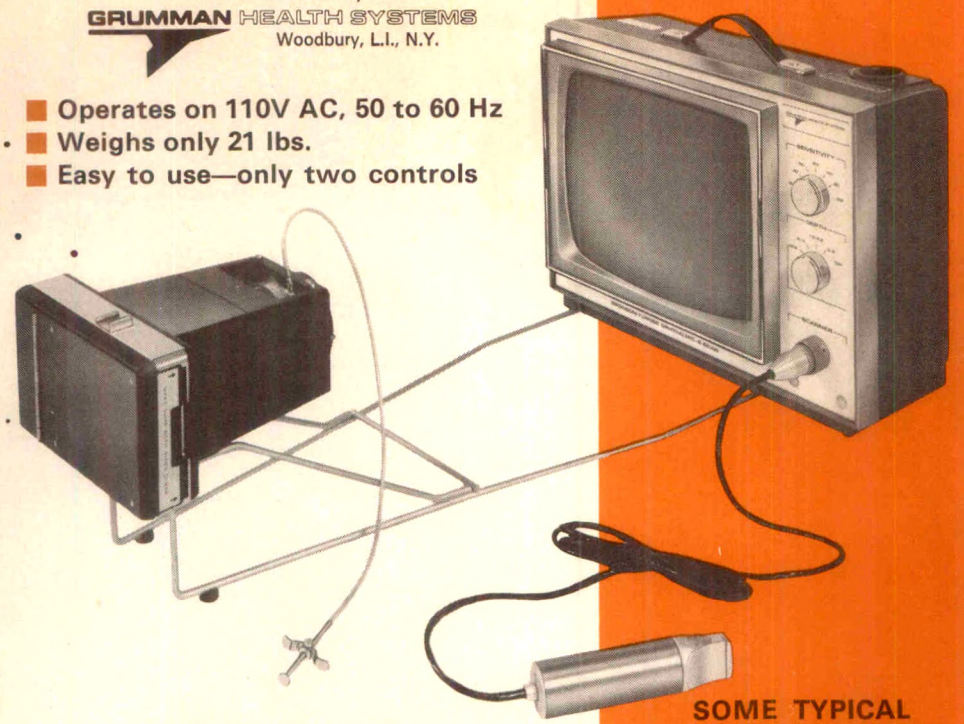
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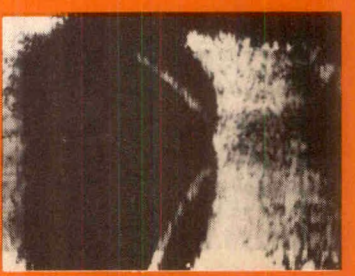
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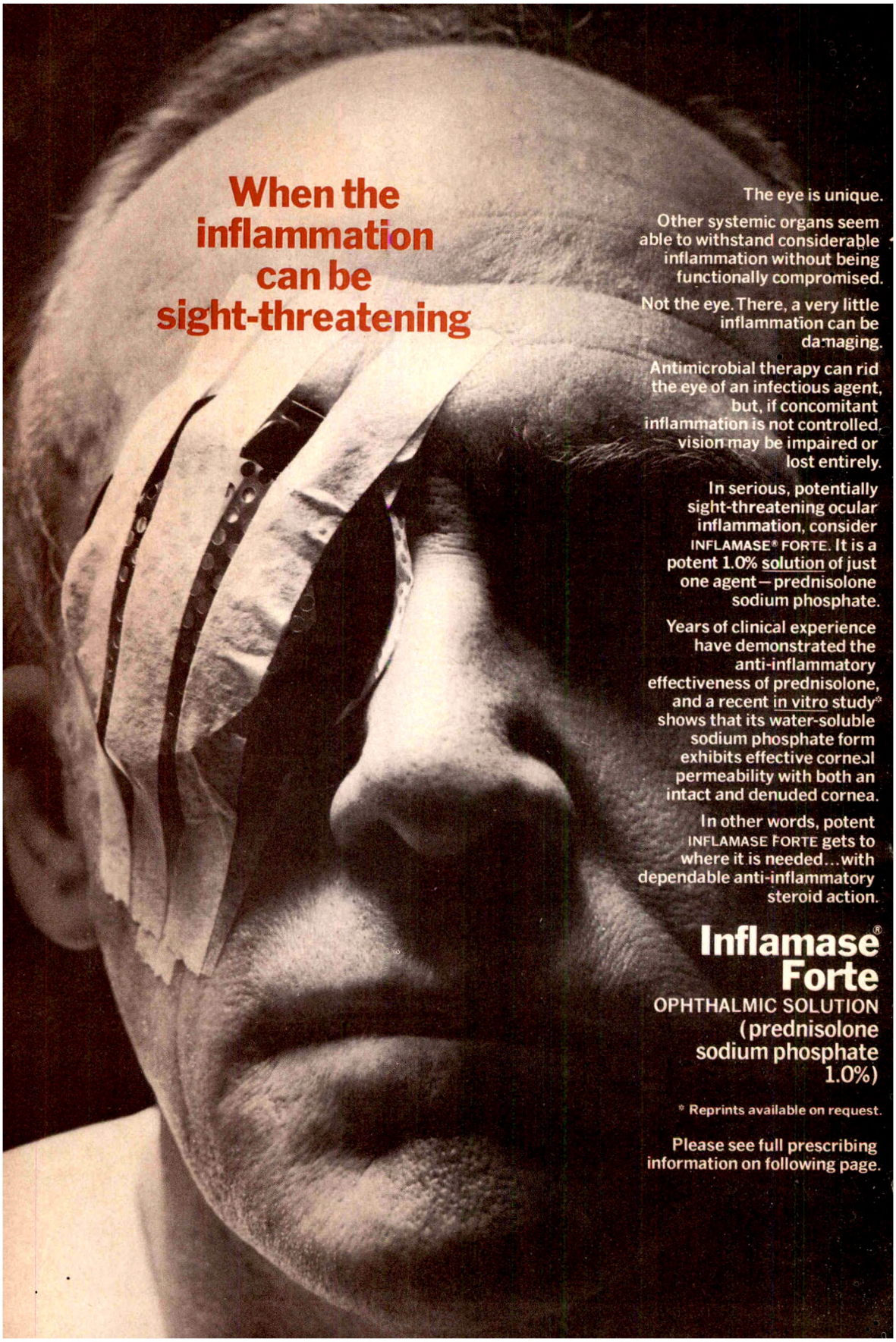


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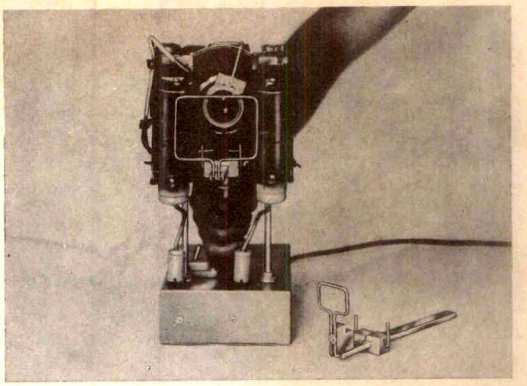
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AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY ANNUAL MEETING

The 1975 meeting of the American Academy of Ophthalmology and Otolaryngology will be held in Dallas, Sept. 21-25, 1975. The Section on Ophthalmology program to be presented is as follows:

Monday, Sept. 22, 9 A.M. to 12:30 P.M.

Convention Center Arena

Presiding Officer: Frank W. Newell, President

Secretary: F. C. Blodi

9 A.M.

OPENING OF THE SESSION

Frank Newell

9:05 A.M.

RECIPIENTS FOR HONOR AWARDS 1975

9:15 A.M.

PRESENTATION OF THE 1975 ANNUAL AWARD TO A LAY PERSON

9:20 A.M.

PRESIDENTIAL ADDRESS

Frank Newell

9:40 A.M.

ADDRESS BY THE GUEST OF HONOR
NEW DIMENSIONS IN OCULAR PHARMACOLOGY 1975

Irving H. Leopold

10 A.M.

CIRCULATORY CHANGES AT THE OPTIC NERVE HEAD

(Movie)

Kenneth C. Swan

10:10 A.M.

A COMPARISON OF CAROTID COMPRESSION TONOGRAPHY AND OPHTHALMODYNAMOMETRY WITH ARTERIOGRAPHY: A PROSPECTIVE STUDY

David N. Cohen and Richard Wangelin

10:20 A.M.

RADIOGRAPHIC EXOPHTHALMOMETRY

Michael Schermer, Hugo Bogren, and Charles Franti

10:30 A.M.

THE XXXII JACKSON MEMORIAL LECTURE
THE PATHOLOGY OF ORBITAL BONES

F. C. Blodi

10:50 A.M.

EXOPHTHALMOS: COMPUTERIZED TOMOGRAPHY AND B-SCAN ULTRASONOGRAPHY

Sadek Hilal, Stephen L. Trokel, and D. Jackson Coleman

11 A.M.

COMPARISON OF ULTRASONOGRAPHY, COMPUTERIZED TOMOGRAPHY (EMI SCAN), AND RADIOGRAPHIC TECHNIQUES IN EVALUATION OF EXOPHTHALMOS

Richard L. Dallow, K. Jack Momose, and Alfred Weber

11:10 A.M.

COMPUTERIZED AXIAL TRANSVERSE TOMOGRAPHY IN THE DIAGNOSIS OF ORBITAL TUMORS

Lawrence D. Jacobs and William R. Kinkel

11:20 A.M.

A NEW METHOD FOR LOCALIZATION OF INTRAORBITAL FOREIGN BODIES

Hugo Bogren, Gösta Elfström, Björn Tengroth, and Thomas Newton

11:30 A.M.

SUBRETINAL TRACKS IN OPHTHALMOMYIASIS

J. Donald M. Gass and Richard A. Lewis

11:40 A.M.

THE EVALUATION AND TREATMENT OF SUPERIOR OBLIQUE PALSY

David Mittelman and Eugene R. Folk

11:50 A.M.

DENERVATION OF THE INFERIOR OBLIQUE: CURRENT STATUS AND LONG-TERM RESULTS

Caleb Gonzalez

NOON

VITRECTOMY BY ULTRASONIC FRAGMENTATION

Louis J. Girard

12:10 P.M.

SPECTRUM OF TRABECULAR PIGMENTATION

Merlyn M. Rodrigues, George L. Spaeth, Stanley Weinreb, and E. Sivalingam

12:20 P.M.

IATROGENIC BREAKS IN BRUCH'S MEMBRANE IN CHOROIDAL MELANOMA

Thomas C. Burton

Tuesday, Sept. 23, 9 A.M. to 12:35 P.M.

Convention Center Arena

Presiding Officer: Albert D. Ruedemann, Jr., Second Vice-President

Secretary: F. C. Blodi

9 A.M.

QUANTITATIVE LACRIMAL SCINTILLOGRAPHY

J. J. Hurwitz

9:10 A.M.

CONTRAST DACRYOCYSTOGRAPHY VERSUS TECHNETIUM 99m LACRIMAL SCAN

Gerald Saparoff, Tapan Chaudhuri, Tuhin Chaudhuri, Kenneth Dolan, and J. H. Christie

9:20 A.M.

SIMULTANEOUS NOSOCOMIAL AND COMMUNITY OUTBREAK OF EPIDEMIC KERATOCONJUNCTIVITIS WITH TYPE 8 AND TYPE 19 ADENOVIRUS

David W. Vastine, Carole E. West, Herbert Yamashiroya, David I. Gieser, Roberta Smith, Donna D. Saxton, and Maurice A. Mufson

9:30 A.M.

VIDARABINE THERAPY OF SIMPLE AND IDU-COMPLICATED HERPETIC KERATITIS

Deborah Pavan-Langston

9:40 A.M.

IMMUNOFLUORESCENT STUDIES OF OCULAR CICATRICIAL PEMPHIGOID

Nancy Furey, Carole West, Thomas Andrews, Promila Daman Paul, and Samuel F. Bean

9:50 A.M.

IRIDOCORNEAL ADHESIONS IN POSTERIOR POLYMORPHOUS DYSTROPHY

Gerhard W. Cibis and Jay H. Krachmer

10 A.M.

PATHOGENESIS AND TREATMENT OF PERSISTENT EPITHELIAL DEFECTS

H. Dwight Cavanagh, Don H. Pillaja, Richard A. Thoft, and Claes H. Dohlman

10:10 A.M.

CLINICAL SPECULAR MICROSCOPY

William M. Bourne, Bernard E. McCarey, and Herbert E. Kaufman

10:20 A.M.

PENETRATING KERATOPLASTY USING ORGAN CULTURED CORNEA

Donald J. Doughman, John Harris, and Mary Kay Schmitt

10:30 A.M.

SCIENTIFIC EXHIBIT AWARDS

10:35 A.M.

SYMPOSIUM: THE OPTIC DISK IN GLAUCOMA

Chairman: Bernard Schwartz

ANATOMY AND PATHOLOGY OF THE OPTIC DISK IN GLAUCOMA

Paul Henkind

CIRCULATION OF THE OPTIC DISK

Sohan Singh Hayreh

NORMAL VARIATIONS OF THE OPTIC DISK

Peter Kronfeld

DISK CHANGES IN GLAUCOMA

George L. Spaeth

CORRELATION BETWEEN OPTIC DISK CHANGES AND VISUAL FIELD CHANGES

Stephen M. Drance

NEW TECHNIQUES FOR THE EXAMINATION OF THE OPTIC DISK AND THEIR CLINICAL APPLICATONS

Bernard Schwartz

11:35 A.M.

PHOTOGRAMMETRIC ANALYSIS OF THE THREE DIMENSIONAL GEOMETRY OF NORMAL AND GLAUCOMATOUS OPTIC CUPS

Gerald L. Portney

11:45 A.M.

ANGLE-CLOSURE GLAUCOMA FOLLOWING SCLERAL BUCKLING OPERATIONS

Rodolfo N. Perez, Charles D. Phelps, and Thomas C. Burton

11:55 A.M.

THE VASCULAR PATHOGENESIS OF GLAUCOMATOUS OPTIC NERVE DISEASE

J. Terry Ernest

12:05 P.M.

COMBINED CYCLODIALYSIS AND CATARACT EXTRACTION

M. Bruce Shields and Richard J. Simmons

12:15 P.M.

VISUAL FIELD PROGRESSION IN OPEN-ANGLE GLAUCOMA PRESENTING WITH MONOCULAR FIELD LOSS

Thomas S. Harbin, Jr., Steven M. Podos, and Bernard Becker

12:25 P.M.

A COMPARISON OF PATIENT COMPLIANCE IN TREATED VS. UNTREATED OCULAR HYPERTENSION

John F. Bigger

5:45 P.M.

THE ANNUAL BUSINESS MEETING

Tuesday, Sept. 23, 9 A.M.

The Theater

Combined Session with the Committee on Plastic and Reconstructive Surgery

Presiding: Frank W. Newell, President

Chairman of Committee on Plastic and Reconstructive Surgery: Robert B. Wilkins

OCULOPLASTIC COMPLICATIONS—PREVENTION AND TREATMENT

COMPLICATIONS OF BLOW-OUT FRACTURE SURGERY

Jared M. Emery

ESSENTIAL BLEPHAROSPASM: PROBLEMS AND COMPLICATIONS

Bartley R. Frueh

COMPLICATIONS OF BLEPHAROPLASTY

Eugene Wiggs

INTRODUCTION OF THE WENDELL L. HUGHES LECTURER

Crowell Beard

WENDELL L. HUGHES LECTURE
OPHTHALMIC PLASTIC SURGERY

Orkan Stasior

EYELID RECONSTRUCTION PROBLEMS—
UPPER EYELID—NON-MUSTARDÉ

Byron Smith

EYELID RECONSTRUCTION PROBLEMS—
LOWER EYELID—NON-MUSTARDÉ

Charles Beyer

EYELID RECONSTRUCTION PROBLEMS—
MUSTARDÉ TECHNIQUES

John Mustardé

PROBLEMS IN LACRIMAL SURGERY:
DACRYOCYSTORHINOSTOMY

James Langham

PROBLEMS IN LACRIMAL SURGERY: TUBES

John Wobig

SOCKET RECONSTRUCTION—WHAT REALLY HAPPENS

Richard Dortzbach

THE EXTRUDING IMPLANT

Clinton McCord

TREATMENT OF ACUTE EYELID TRAUMA TO PREVENT LATE COMPLICATIONS

Robert R. Waller

TREATMENT OF LATE TRAUMATIC EYELID PROBLEMS

David B. Soll

PROBLEM CASES SYMPOSIUM

Moderator: Robert B. Wilkins

Panel: Alston Callahan, Charles Iliff, Byron Smith, and Richard Tenzel

5:45 P.M.

THE ANNUAL BUSINESS MEETING

Convention Center Arena

Wednesday, Sept. 24, 9 A.M. to 12:30 P.M.

Convention Center Arena

Presiding Officer: Frank W. Newell, President

Secretary: F. C. Blodi

9 A.M.

PROGNOSIS OF SENILE RETINOSCHISIS

Norman E. Byer

9:10 A.M.

ROUND ATROPHIC HOLES IN LATTICE DEGENERATION, AN IMPORTANT CAUSE OF PHAKIC RETINAL DETACHMENT

William V. Tillery and Alfred C. Lucier

9:20 A.M.

RETINAL DETACHMENTS SECONDARY TO RETINAL BRANCH VEIN OCCLUSIONS

F. A. Gutman and H. Zegarra

9:30 A.M.

INSULIN-INDUCED IMMUNOGENIC RETINOPATHY RESEMBLING THE RETINITIS PROLIFERANS OF DIABETES

Alan L. Shabo and D. S. Maxwell

9:40 A.M.

THE MISDIAGNOSIS OF CENTRAL SEROUS CHORIORETINOPATHY

Howard Schatz, Kurt Gitter, and Lawrence Yannuzzi

9:50 A.M.

ACUTE MACULOPATHIES

August F. Deutman

10:05 A.M.

CLINICAL EXPERIENCE WITH PRESUMED HEMANGIOMA OF THE CHOROID: RADIO-ACTIVE PHOSPHORUS (^{32}P) UPTAKE STUDIES AS AN AID IN DIFFERENTIAL DIAGNOSIS

William H. Jarrett II, William S. Hagler, James H. Larose, and Jerry Shields

10:15 A.M.

ECHOGRAPHIC DIAGNOSIS OF CHOROIDAL HEMANGIOMAS

Karl C. Ossoinig

10:25 A.M.

NONOCULAR CANCER IN RETINOBLASTOMA SURVIVORS

David H. Abramson, Robert M. Ellsworth, and Lorenz E. Zimmerman

10:35 A.M.

LIPOFUSCIN PIGMENT OVER BENIGN AND MALIGNANT CHOROIDAL TUMORS

Jerry A. Shields, Merlyn M. Rodrigues, Lov K. Sarin, William S. Tasman, and William H. Annesley, Jr.

10:45 A.M.

CONSERVATIVE MANAGEMENT OF MALIGNANT MELANOMA OF THE CHOROID: FOLLOW-UP STUDY OF PATIENTS TREATED WITH IRRADIATION

Frederick H. Davidorf, Torrence A. Makley, and Janet R. Lang

10:55 A.M.

THE PENDULUM OF PROGRESS

Stephen J. H. Miller

11:10 A.M.

SYMPOSIUM: PARS PLANA VITRECTOMY

Chairman: Robert Machemer

PRINCIPLES OF INSTRUMENTATION

Stephen Ryan

PREOPERATIVE EVALUATION

Felipe I. Tolentino

LENS REMOVAL

Nicholas Douvas

ANTERIOR SEGMENT RECONSTRUCTION

Ronald Michels

VITREOUS OPACITIES

Gholam Peyman

DIABETIC RETINOPATHY

Franklin L. Myers

RETINAL DETACHMENT

Thomas M. Aaberg

PERFORATING INJURIES AND INTRAOCULAR FOREIGN BODIES

D. Jackson Coleman and William Hutton

PRERETINAL MEMBRANES

Robert Machemer

FUTURE HORIZONS

Allan E. Kreiger

Wednesday, Sept. 24, 9 A.M. to 12:30 P.M.

The Theater

Combined Session with the Association for Research in Vision and Ophthalmology

Presiding: Albert D. Ruedemann, Jr., Second Vice-President

Secretary: Robert Reinecke

Co-Chairmen: R. W. Bellhorn and Paul Henkind

9 A.M.

SYMPOSIUM ON DISEASES OF UNKNOWN ETIOLOGY: THE CONTRIBUTION OF ANIMAL STUDIES TO THEIR UNDERSTANDING

9:05 A.M.

KERATOCONJUNCTIVITIS SICCA
THE HUMAN PROBLEM
Jules L. Baum

THE DISEASE IN THE DOG
Lloyd C. Helper

9:25 A.M.

VIRUS KERATOPATHY
THE HUMAN PROBLEM
Herbert E. Kaufman

THE DISEASE IN CATS
Stephen I. Bistner

9:45 A.M.

GLAUCOMA
ANIMAL MODELS OF HUMAN GLAUCOMA
Steven M. Podos

THE DISEASE IN THE BEAGLE
Kirk N. Gelatt

THE DISEASE IN BASSETT HOUND
Milton Wyman

10:20 A.M.

RETINAL DEGENERATIONS
CONE DYSFUNCTION SYNDROMES IN MAN
Ronald E. Carr and Irwin M. Siegel

RETINITIS PIGMENTOSA AND ALLIED RETINAL DISEASES:
ELECTROPHYSIOLOGICAL STUDIES
Eliot L. Berson

RETINAL DEGENERATION IN THE TAURINE DEFICIENT CAT:
BIOCHEMICAL AND ELECTROPHYSIOLOGICAL FINDINGS
Susan Schmidt, Eliot L. Berson, and K. C. Hayes

HEMERALOPIA IN DOGS
Lionel F. Rubin

FELINE CENTRAL RETINAL DEGENERATION
Roy W. Bellhorn

INHERITED RETINAL DEGENERATIONS IN THE DOG
Gustavo D. Aguirre

11:15 A.M.

DIABETIC RETINOPATHY
THE HUMAN PROBLEM
George H. Bresnick

THE DISEASE IN ANIMALS
Ronald Engerman

11:35 A.M.

RETINITIS PROLIFERANS—RETINAL DETACHMENT
THE HUMAN PROBLEM
H. Mackenzie Freeman

COLLIE EYE SYNDROME
Richard H. Donovan

11:55 A.M.

CONE-ROD DYSTROPHIES
THE HUMAN PROBLEM
Gerald Fishman

THE DISEASE IN BABOONS

Samuel J. Vainisi and E. Dan Wolfe

12:15 P.M.

DISCUSSION AND CONCLUDING REMARKS

Roy W. Bellhorn

Thursday, Sept. 25, 9 A.M.

Convention Center Arena

Presiding Officer: Frank W. Newell, President

Secretary: F. C. Blodi

9 A.M.

PRESENTATION OF NEW INSTRUMENTS

Sphincterotomy Scissors, Jules L. Baum

Double Simultaneous Aspirating Irrigating Syringes, Jose Berrocal

Lens Holder, Jose Berrocal

Indirect Fundus Camera, Frederick H. Davidorf and William Plummer

An Irrigating Lens Implant Holder, Robert C. Drews

A Micro Iris Retractor, Robert C. Drews

Aspiration Control, J. Terry Ernest and John L. Trimble

Minimal Ptosis Clamp, Paul T. Gavaris

Lacrimal Duct Probing Light, Paul T. Gavaris

Full Thickness Eyelid Excision Clamp (Bethesda-Gavaris Clamp), Paul T. Gavaris

Assistant Microscopes, Louis J. Girard

Orange Peel Orbital Implant, Pierre Guibor

VII Nerve Replacement Kit, Pierre Guibor

Surgical Eye Shields, Pierre Guibor

A New Phako Liquification Cryoprobe, Heskel M. Haddad

Suture Snipper, G. Peter Halberg

An Improved Method of Visualizing and Photographing Corneal Staining, Johnny Justice, Jr., and Joseph W. Soper

A New Binocular Scotometer, Emanuel Krimsky

A New Machine for Irrigation Aspiration, David Pao

Modified Stereo Viewer, Howard Schatz

Closed Circuit TV Magnification of Fluorescein Angiography, Stanley S. Schocket and Emery Billings

Fiber Optic Conjunctivorhinostomy Probe, Hampson A. Sisler

Laser Trabeculotomy, Zarko M. Vucicevic and Robert Webb

The Double Ring Support: An Instrument to Insure Safety With Scleral Buckling After Cataract Extraction, R. Sloan Wilson

Retinal Cryoring: A New Instrument for Retinal Surgery, R. Sloan Wilson

9:20 A.M.

EARLY ACUTE IRITIS AFTER CATARACT EXTRACTION

Henry F. Allen and Arthur S. Grove, Jr.

9:30 A.M.

TREATMENT OF POSTCATARACT BACTERIAL ENDOPHTHALMITIS WITH PERIOCULAR AND SYSTEMIC ANTIBIOTICS AND CORTICOSTEROIDS

Jules L. Baum and Gullapalli N. Rao

9:40 A.M.

OPPORTUNISTIC VIRAL AND BACTERIAL PATHOGENS IN OCULAR INFECTIONS

Phillips Thygeson and Masao Okumoto

9:50 A.M.

CATARACT SURGERY BY THE INTRACAPSULAR METHODS AND BY PHACOEMULSIFICATION

Edward Cotlier and Marc Rose

10 A.M.

CATARACT EXTRACTION DURING ACUTE ATTACK OF PHACOLYTIC GLAUCOMA

Moshe Lazar, Rivka Bracha, and Pinhas Nemet

10:10 A.M.

LATE HYPHEMA DUE TO WOUND VASCULARIZATION AFTER CATARACT EXTRACTION

Kenneth C. Swan

10:20 A.M.

MAINTENANCE OF THE ANTERIOR CHAMBER DURING PENETRATING KERATOPLASTY

Steven G. Kramer

10:30 A.M.

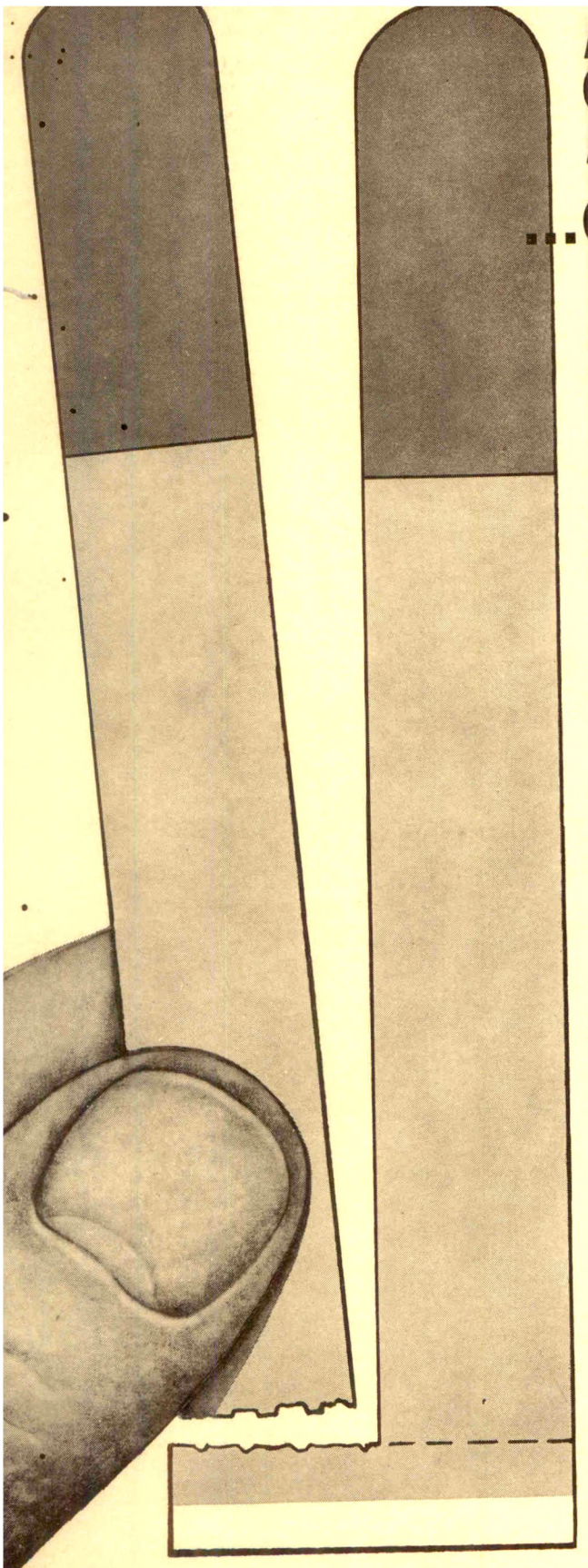
RELEASE OF ANTERIOR SEGMENT VITREOUS STRANDS (Movie)

John R. Lynn

10:40 A.M.

SYMPOSIUM: INTRAOCULAR LENSES

Chairman: Edward W. D. Norton
Participants: Harold Ridley, C. D. Binkhorst, Jorge Draeger, Lee Duffner, S. Fyodorov, Henry Hirschman, Norman Jaffe, Michael Roper-Hall, and Jan Worst

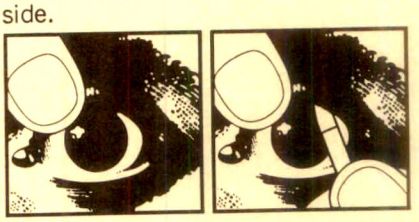


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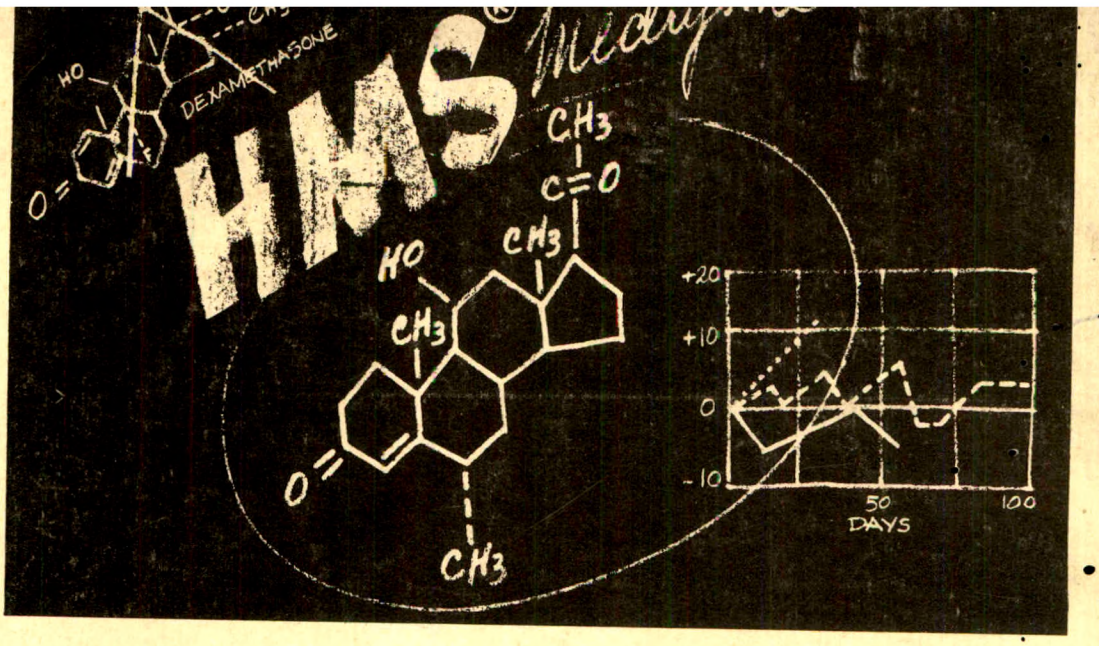
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WARNINGS 1. Acute purulent untreated infections of the eye may be masked, enhanced or activated by the presence of steroid medication. 2. Corneal or scleral perforation occasionally has been reported with prolonged use of topical steroids. In high dosage they have been associated with corneal thinning. 3. Prolonged use of topical steroids may increase intraocular pressure, with possible resultant glaucoma, damage to the optic nerve, and defects in visual acuity and fields of vision. However, data from 2 uncontrolled studies[1-2] indicate that in patients with increased intraocular pressure and in those susceptible to a rise in intraocular pressure upon application of topical steroids, there is less effect on pressure with HMS than with dexamethasone or betamethasone. 4. Prolonged use of topical corticosteroids may rarely be associated with development of posterior subcapsular cataracts. 5. Systemic absorption and systemic side effects may result with the use of topical steroids. 6. HMS® (medrysone) is not recommended for use in iritis and uveitis as its therapeutic effectiveness has not been demonstrated in these conditions. 7. Steroid medication in the presence of stromal herpes simplex requires great caution; frequent slit lamp microscopy is suggested. 8. Prolonged use may aid in the establishment of secondary ocular infections from fungi and viruses liberated from ocular tissue. Use in Pregnancy: The use of topical steroids in pregnancy should be limited to conditions serious enough to warrant such treatment, so that possible risk to the fetus may be justified by the expected benefit to the mother.

PRECAUTIONS With prolonged use of HMS (medrysone) the intraocular pressure and lens should be examined periodically. In persistent corneal ulceration where a steroid has been used, or is in use, fungal infection should be suspected.

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AJOPAA 79 (3) 327-484 (1975)

VOLUME 80 NUMBER 3, PART I SEPTEMBER, 1975

AMERICAN JOURNAL OF OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON



MICHAEL J. HOGAN

During the past three decades Professor Michael J. Hogan has been a prodigiously productive investigator, dynamic leader, and outstanding contributor to all phases of American ophthalmology. After succeeding Frederick C. Cordes as chairman, Professor Hogan established a remarkably successful Department of Ophthalmology at the University of California in San Francisco. Under his aegis the Proctor Laboratory became a leading center for ophthalmic research, and he and his colleagues played a major role in advancing studies in many phases of ophthalmic science. He surrounded himself with superior ophthalmologists and scientists and as he became emeritus professor of ophthalmology on June 30, 1975, he could observe a large group of dedicated and competent clinicians and investigators who will continue his studies both at the University of California and at high posts throughout the world.

His investigations have led to contributions in almost every phase of ophthalmology. His "Histology of the Human Eye," written with Alvarado and Weddell, provides a successor to Maximilian Salzmann's "Anatomy of the Eye." It seems likely to duplicate the earlier volume in enduring more than a half century. "Ophthalmic Pathology," edited by Michael J. Hogan and Lorenz E. Zimmerman, has been an introduction for two generations of ophthalmologists and will shortly appear in a third edition.

Mike has served faithfully in positions of responsibility. With this supplement the directors of the Ophthalmic Publishing Company hope to indicate their admiration and respect for Dr. Hogan's accomplishments as he passes on to another career that, with more time at his disposal, promises to be as sparkling and productive as the past.

The directors are grateful to Professor Hogan's friend and collaborator and now director of the Proctor Laboratories, Professor G. Richard O'Connor, who is responsible for the preparation of this volume.

THE OPHTHALMIC PUBLISHING COMPANY DIRECTORS
A. Edward Maumenee
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AMERICAN JOURNAL OF OPHTHALMOLOGY

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THE AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, 233 East Ontario Street, Chicago, Illinois 60611. The subscription rate in the United States is $15.00 yearly; in Canada and all other foreign countries, the rate is $18.00 (U.S.) yearly. Subscription and Advertising Office: The Ophthalmic Publishing Company, 233 East Ontario Street, Chicago, Illinois 60611. Copyright, 1975, Ophthalmic Publishing Company, 233 East Ontario Street, Chicago, Illinois 60611. Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A.

AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 80 SEPTEMBER, 1975 NUMBER 3, PART I

MICHAEL J. HOGAN, M.D.

On June 30, 1975, Michael J. Hogan retired from his position as professor and chairman of the Department of Ophthalmology at the University of California, San Francisco. Those of us who have been associated with him in one capacity or another feel a keen sense of debt to Michael Hogan as well as a lasting appreciation for his many contributions to academic ophthalmology. This issue of the AMERICAN JOURNAL OF OPHTHALMOLOGY is dedicated to an extraordinary physician, a true basic scientist, and a beloved teacher.

Michael Hogan was well established in the private practice of general surgery in San Diego, California, when he made the decision to specialize in ophthalmology. Urged onward, surely by his wife Vera Merrill Hogan and by his father-in-law who was an ophthalmologist in San Diego, he entered the eye residency program at the University of California (under the direction of the late Frederick C. Cordes) in 1938. At the completion of his clinical training in ophthalmology he pursued additional research training at the Illinois Eye and Ear Infirmary in Chicago and at the Eye Institute of the Columbia-Presbyterian Medical Center in New York, where he became especially interested in ocular tumors. Returning to California ("the Promised Land") in 1941, he joined the faculty of the Eye Department at the University of California where he has continued to work for over 30 years, interrupted only by a three-year period of service in the Navy during World War II.

Early in his career, Dr. Hogan developed a profound interest in ocular pathology, heading the department's Eye Pathology Laboratory from 1946 to 1959, and coauthoring a now famous textbook, "Ocular Pathology," which is soon to appear in its third edition. His extensive knowledge of pathology paved the way for his numerous and penetrating studies of ocular toxoplasmosis. Indeed, he has done more than any other ophthalmologist in this country to advance our knowledge of the clinical and laboratory aspects of this disease. His monograph on this subject, published by the Columbia University Press in 1951, is a classic that established his eminence in the field, and it is still an excellent primer for those interested in the subject.

Of his clinical interests, those connected with uveitis and with tumors of the eye have stimulated him to produce the greatest number of papers. With Phillips Thygeson and Samuel J. Kimura he founded the Uveitis Survey Clinic at the University of California that has now been in operation for over 25 years. Having compiled data on the history, the physical findings, and the laboratory investigation of more than 5,000 patients with various types of uveitis, Michael Hogan was in a position to write definitive papers on such subjects as chronic cyclitis, uveitis associated with inflammatory joint disease, and toxoplasmosis.

In the late 1950s Dr. Hogan was one of the first few investigators in the United States to study the fine structural anatomy of the eye with the electron microscope.

These studies culminated in the production of another classic textbook, "Histology of the Human Eye," which has served students of ophthalmology and researchers in many different areas of visual science as a basic, detailed text. Since its completion, Dr. Hogan has done studies on the fine structure of a number of disease states such as dystrophies of the cornea, malignant tumors of the eye and orbit, and degenerations of the macula.

In the field of public service Michael Hogan has served on the editorial boards of Investigative Ophthalmology, THE AMERICAN JOURNAL OF OPHTHALMOLOGY, and the Archives of Ophthalmology. He was a member of the Board of Trustees of the American Medical Association and served its Section on Ophthalmology in several capacities in addition to being its representative to the International Federation of Ophthalmological Socities.

He has contributed greatly to the activities of the American Ophthalmological Society, the Association for Research in Vision and Ophthalmology, and the Association of University Professors of Ophthalmology, on whose Board of Trustees he served as chairman in 1970. He was president of the Pacific Coast Oto-Ophthalmological Society and vice-president of the International Council of Ophthalmology.

Dr. Hogan served as the first director of the Francis I. Proctor Foundation for Research in Ophthalmology at the University of California from 1951 to 1959, at which time he surrendered this position to take over the chairmanship of the Department of Ophthalmology. He has continued to make valuable research contributions to the foundation and serves on its board of governors.

Michael Hogan is the recipient of numerous awards and prizes and has given public presentations under the auspices of virtually all of the named ophthalmic lectureships available in this country and in Europe, including the Jackson Lecture in 1957, the Howe Lecture in 1960, the Arthur Bedell Lecture in 1961, and the Walter Wright Lecture (University of Toronto) in 1961. He received the Proctor Gold Medal in 1963, the Knapp Prize in 1966, the Outstanding Civilian Service Medal from the Surgeon General in 1967, the Bowman Medal in the same year, and the Howe Medal in May 1975.

Those of us who have been close to Mike in the sphere of academic ophthalmology, in general, and in the affairs of the University of California, in particular, wish to do him one additional honor. With the approval of the Ophthalmic Publishing Company and the best wishes of the chief editor of the JOURNAL, Frank W. Newell, we wish to dedicate this issue to Michael J. Hogan as a token of our love and esteem.

G. RICHARD O'CONNOR

CURRICULUM VITAE OF MICHAEL J. HOGAN

Born: Aug. 26, 1907, Kemmerer, Wyoming

EDUCATION:

A.B. University of Utah, 1930

M.D. Cornell University Medical School, New York, 1932

POSTGRADUATE EXPERIENCE AND APPOINTMENTS

1932-1933 Paterson General Hospital, Paterson, New Jersey, Intern

1933-1935 Bellevue Hospital, New York, Resident Surgeon

1935-1938 San Diego, California, private practice

1938-1940 University of California Hospital, San Francisco, Resident in Ophthalmology

1940-1941 Illinois Eye and Ear Infirmary, Chicago, Research

1941 (Apr.-Aug.) Columbia University, Department of Ophthalmology, Research

1941-1943 University of California Hospital, San Francisco, Clinical Instructor—Ophthalmology

1942 Certified: American Board of Ophthalmology

1943-1946 United States Navy, Lieutenant (Lt. CDR)

1946-1948 University of California Hospital, San Francisco, Assistant Clinical Professor, Ophthalmology

1946-1959 University of California Medical Center, Chief, Eye Pathology Laboratory

1948-1964 University of California Medical Center, Director, U.C. Eye Bank
1948-1951 University of California School of Medicine, Associate Clinical Professor of Ophthalmology
1951-1959 University of California School of Medicine, Director, Francis I. Proctor Foundation for Research in Ophthalmology
1951-1959 University of California School of Medicine, Vice-Chairman, Department of Ophthalmology
1950-1957 University of California School of Medicine, Clinical Professor of Ophthalmology
1957 University of California School of Medicine, Professor of Ophthalmology
1959 University of California School of Medicine, Chairman, Department of Ophthalmology
1967-1968 University of Rome, Rome, Italy (sabbatical), NIH Special Fellow—Research on Uveitis

PROFESSIONAL ACTIVITIES

Consultant in Ophthalmology:
Ft. Miley Veterans Administration Hospital, San Francisco
Letterman General Hospital, San Francisco
Laguna Honda Home, San Francisco
San Francisco General Hospital
Oak Knoll Naval Hospital, Oakland
Regional Consultant Surgical Service; Veterans Administration Hospital, Washington, D.C. for Northern California, Nevada, and Utah
Editorial Board:
Investigative Ophthalmology, St. Louis
American Medical Association specialty journals
Member, Editorial Board, AMERICAN JOURNAL OF OPHTHALMOLOGY
Director, Ophthalmic Publishing Co. 1969-
Associate Editor:
Archives of Ophthalmology, Chicago
American Medical Association:
Section on Ophthalmology, Committee on Eye Banks
Representative for National Committee on Research in Ophthalmology and Blindness
Knapp Medal Committee
Board of Trustees
Representative to the International Federation of Ophthalmological Societies 1970-1971
American Ophthalmological Society, 1950
Committee on Theses 1965-1968
Howe Medal, 1975
Association of University Professors of Ophthalmology:
Trustee, 1965-
Chairman, Board of Trustees, 1970
American Board of Ophthalmology (Member), 1958-1964
Consultant, 1964-
American Academy of Ophthalmology and Otolaryngology:
Councillor
Chairman, Ophthalmic Pathology Committee
Representative on Advisory Committee to Armed Forces Institute of Pathology
Chairman Academy Committee
American College of Surgeons:
Fellow, 1960
Committee on Applicants for District 1, Northern California
Governor, 1964-1968
Association for Research in Ophthalmology, Inc.:
Committee on Eye Banks, 1953
Board of Trustees, 1953-1959
Chairman, Board of Trustees, 1957-1958
Nominating Committee of the Board of Trustees, 1960
Proctor Award Committee
President, Association for Research in Ophthalmology, Western Section, 1971-1972
California Medical Association:
Member 1936
California State Department of Public Health:
Prevention of Blindness Project, Advisory Committee
Heed Ophthalmic Foundation, 1965-
Chairman, Board of Directors 1967-1975
International Eye Film Library:
Consultant, 1963
Advisory Committee, 1966
National Advisory Council to the Ophthalmological Foundation, 1957-1963
National Advisory Council to the Eye Bank for Sight Restoration, New York
National Council to Combat Blindness, Scientific Advisory Committee, New York
National Association on Standard Medical Vocabulary, 1964
National Aid to the Visually Handicapped, 1964
National Institute of Neurological Diseases and Blindness, Bethesda, Maryland:
Committee on Uveitis
National Advisory Council
Selection Committee
National Medical Foundation for Eye Care, Board of Trustees, 1959-1961
National Society for the Prevention of Blindness, New York:
Board of Directors—Executive Committee, Consultant
Committee on Basic and Clinical Research
Northern California Society for the Prevention of Blindness, San Francisco:
President, 1965
Chairman, Medical Advisory Committee, Bay Area Project, 1966
Ophthalmic Pathology Club, Washington, D.C. (Changed to Verhoeff Society, 1965), Member, 1947-
Pan-American Congress of Ophthalmology:
Board of Directors
Executive Committee
Western Ophthalmic Pathology Club, Member, 1957–
San Francisco Medical Society:
Chairman, Eye Section, 1959-1960
Member of Professional Relations Committee, 1960-1961
Representative to Visual Screening Program
San Francisco Ophthalmological Round Table:

Member, 1945
President, 1958-1959
Vice-President, 1952-1953
Eye Bank Association of America, Consultant, West Coast Eye Bank Committee, 1964
Founder: University of California Eye Residents Association (name changed to: Frederick C. Cordes Eye Society), Director, 1948
Pacific Coast Oto-Ophthalmological Society, 1947
Chairman of Instruction, 1955-1956
President, 1968-1969
San Francisco Diabetes Association, 1964
American Medical Association Political Action Committee, 1964
Knights' Templar Eye Foundation, Ophthalmologist-Advisor, 1966
International Council of Ophthalmology, Vice-President, 1970-1974
Seeing Eye, Inc., Member, Grants Advisory Committee 1973-
Member: Western Society for Clinical Research, French Ophthalmological Society
Honorary Member: Arizona Ophthalmological Society, 1965
Midwestern Clinical Society
Advisory Consultant: California Medical Eye Council
Honorary Consultant: Armed Forces Institute of Ophthalmology, Washington, D.C.
That Man May See, Inc., Vice-President, 1972-
Ophthalmic Publishing Co., Vice-President, May 31, 1975.

LECTURES AND AWARDS

Dec. 18, 1952—Fourth Curran Lecture, Kansas City, Missouri, "Uveitis syndromes. Their relationship to systemic disease"
Nov. 5, 1953—Fourth Estelle Doheny Lecture, Los Angeles, California, "Studies on ocular toxoplasmosis"
Oct. 16, 1957—American Academy of Ophthalmology and Otolaryngology Meeting, Chicago, XIV Edward Jackson Memorial Lecture, "Ocular toxoplasmosis"
Jan. 31-Feb. 3, 1960—VI Pan-American Congress of Ophthalmology, Guest of Honor, Caracas, Venezuela, "Ocular toxoplasmosis"
April 25-29, 1960—Visiting Professor with Harvard appointment of Visiting Lecturer, Harvard Medical School, Boston, Massachusetts, Howe Lecture: "Uveitis"
Feb. 9-11, 1961—Wills Eye Hospital, Philadelphia, Arthur J. Bedell Lecture, "Cyclitis"
Nov. 17, 1961—University of Toronto, Quebec, Walter W. Wright Lecture, "Present knowledge of the etiology of uveitis"
June 18, 1963—Recipient, Proctor Gold Medal of the Association for Research in Ophthalmology for outstanding research on the eye and its diseases, Atlantic City
June 21-25, 1964—American Medical Association Meeting, San Francisco, Calif. Honorable mention for scientific exhibit, "The limbus," by P. Thygeson, M. Hogan, L. Feeney and B. Togni
Feb. 14, 1965—Honorary Fellowship conferred by the Institute of Medicine of Chicago
Feb. 15, 1965—Seventh William Hamlin Wilder Memorial Lecture of the Institute of Medicine of Chicago, "Toxoplasmosis"; presented at a joint meeting of the Institute of Medicine of Chicago and the Chicago Ophthalmological Society
May 18, 1965—Royal Academy of Medicine of Barcelona, Spain (elected May 18), Honorary Award, "Academico Corresponsal Extranjero"
June 1966—American Medical Association Meeting, Knapp Prize Award for Outstanding Ophthalmology Exhibit "Importance of basement membranes of the eye in disease"
April 19, 1967—87th Annual Congress of the Ophthalmological Society of the United Kingdom Bowman Lecture and Award of Bowman Medal, "Bruch's membrane and macular degeneration"
July 14, 1967—Outstanding Civilian Service Medal awarded by Surgeon General, Department of the Army, for work in connection with Letterman Hospital
March 10, 1968—University of Rome, Vittorian Cavara Lecture, "Ocular toxoplasmosis. A critical review"
April 13-17, 1969—Pacific Coast Oto-Ophthalmological Society Meeting, San Francisco, President's Address, "Ocular toxoplasmosis"
May 14-15, 1970—Jules Stein Institute, University of California Los Angeles, First Jules Stein Lecture, "The aqueous outflow apparatus"
Nov. 19, 1970—College of Physicians, Philadelphia, De Schweinitz Lecture, "The retinal pigment epithelium and Bruch's membrane. Their role in macular disease"
April 2-7, 1972—Pan American Congress of Ophthalmology, Houston, Recipient of the 1972 Gradle Medal, "Pathogenesis of macular diseases"
May 24-26, 1972—Snell Memorial Lecture, New York, Presented talk on "Diagnosis and management of uveitis"
May 11-12, 1973—Chicago Ophthalmological Society, Chicago, Sanford Gifford Lecture, "Fuchs' endothelial dystrophy of the cornea"
June 1-2, 1973—Paul A. Chandler Lecture, Boston; Visiting Professor, Massachusetts Eye and Ear Hospital
July, 1973—Appointed Honorary Member, Royal Academy
Oct. 29, 1973—Estelle Doheny Lecture, Los Angeles, "Malignant melanoma"
May 29, 1975—Howe Medal, American Ophthalmological Society, Hot Springs, Virginia

PUBLICATIONS OF MICHAEL J. HOGAN

Cordes, F. C., and Hogan, M. J.: Ocular ichthyosis. Arch. Ophthalmol. 22:590, 1939.

Cordes, F. C., and Hogan, M. J.: Angiomatosis retinae (Hippel's disease). Arch. Ophthalmol. 23:253, 1940.

Cordes, F. C., and Hogan, M. J.: Dysostosis multiplex (Hurler's disease; lipochondrodysplasia; gargoylism). Report of the ocular findings in five cases, with a review of the literature. Arch. Ophthalmol. 27:637, 1942.

Hogan, M. J., and Crawford, J. W.: Epidemic keratoconjunctivitis (superficial punctate keratitis, keratitis subepithelialis, keratitis maculosa, keratitis nummularis). With a review of the literature and a report of 125 cases. Am. J. Ophthalmol. 25:1059, 1942.

Hogan, M. J.: Epidemic keratoconjunctivitis. War Med. 2:984, 1942.

Hogan, M. J., and Cordes, F. C.: Lipochondrodystrophy (dysostosis multiplex; Hurler's disease). Pathologic changes in cornea in three cases. Arch. Ophthalmol. 32:287, 1944.

Hogan, M. J.: Conjunctivitis with membrane formation. Am. J. Ophthalmol. 30:1495, 1947.

———: Toxoplasmic chorioretinitis. Trans. Pac. Coast Otoophthalmol. Soc. 28:83, 1947.

Fritz, M. H., and Hogan, M. J.: Fat embolization involving the human eye. Am. J. Ophthalmol. 31:527, 1948.

Cordes, F. C., and Hogan, M. J.: Primary malignant melanoma of optic disc. Trans. Am. Ophthalmol. Soc. 46:201, 1948.

Hogan, M. J.: Dacrocystorhinostomy. Trans. Am. Acad. Ophthalmol Otolaryngol. 52:600, 1948.

Cordes, F. C., and Hogan, M. J.: Primary malignant melanoma of the optic disc. Report of a case. Am. J. Ophthalmol. 32:1037, 1949.

Hogan, M. J.: Preparation and sterilization of ophthalmic solutions. Calif. Med. 71:414, 1949.

———: Ocular manifestations. In Symposium: Toxoplasmosis. Trans. Am. Acad. Ophthalmol. Otolaryngol. 54:183, 1950.

Thygeson, P., and Hogan, M. J.: Aureomycin in the treatment of herpes simplex corneae. Am. J. Ophthalmol. 33:958, 1950.

Hogan, M. J., and Dickson, O. C.: Bilateral orbital granuloma simulating a neoplasm. Trans. Am. Acad. Ophthalmol. 54:573, 1950.

Hogan, M. J.: Corneal transplantation. Calif. Univ. Med. Center Bull. 1:319, 1949.

———: ACTH and cortisone. Calif. Med. Univ. Center Bull. 2:17, 1950.

Hogan, M. J., Engleman, E. P., Thygeson, P., and Krupp, M.: Effect of ACTH and cortisone on ocular disease. Am. J. Ophthalmol. 34:73, 1951.

Hogan, M. J.: Diseases of the uveal tract. Arch. Ophthalmol. 45:334, 1951.

———: Ocular toxoplasmosis. Fourth Congr. Pan-Am. Oftalmol. 2:1071, 1952.

———: Pathology of Primary Glaucoma. In Symposium on glaucoma. Fourth Congr. Pan-Am. Oftalmol. 1:322, 1952.

———: Ocular Toxoplasmosis, monograph. New York, Columbia University Press, 1951.

Hogan, M. J., and Chaparro, L.: Ocular Surgery. Translation by H. Arruga. Salvat Editores, South America, 1946; New York, McGraw-Hill Book Co., 1952.

Hogan, M. J.: Diseases of the uveal tract. Arch. Ophthalmol. 47:383, 1952.

———: Diseases of the uveal tract. In Progress in Ophthalmology. New York, Grune and Stratton, 1952, pp. 157-173.

———: Ocular contusions. In Symposium: Ocular injuries. Am. J. Ophthalmol. 35:1115, 1952.

Hogan, M. J., Thygeson, P., and Kimura, S.J.: Ocular toxoplasmosis. Trans. Am. Acad. Ophthalmol. Otolarngol. 56:863, 1952.

Hogan, M. J.: Atopic keratoconjunctivitis. Trans. Am. Ophthalmol. Soc. 50:265, 1952; Am. J. Ophthalmol. 36:937, 1953.

Friedenwald, J. S., Wilder, H. C., Maumenee, A. E., Sanders, T. E., Keys, J. E. L., Hogan, M. J., Owens, W. C., and Owens, E. U.: Ophthalmic Pathology. Atlas and Textbook. Philadelphia, W. B. Saunders, 1952.

Thygeson, P., Hogan, M. J., and Kimura, S. J.: Cortisone and hydrocortisone in ocular infections. Trans. Am. Acad. Ophthalmol. Otolaryngol. 57:64, 1953.

Hogan, M. J.: Ocular complications in brucellosis. In Solanes, M. P.: Editorial. Am. J. Ophthalmol. 36:675, 1953.

———: Diseases of the uveal tract. Arch. Ophthalmol. 49:342, 1953.

Kimura, S. J., Thygeson, P., and Hogan, M. J.: Uveitis in children. Arch. Ophthalmol. 51:80, 1954.

Sherman, R. S. Jr., and Hogan, M. J.: Radiation therapy in diseases of the eye. Calif. Med. 80:83, 1954.

Hogan, M. J.: The role of the general practitioner in the detection of some important eye diseases. J. Omaha Mid-West. Clin. Soc. 1954.

Dailey, M. E., Gordan, G. S., Low-Beer, B. V.A., Naffziger, H. C., and Hogan, M. J.: Pituitary irradiation for bilateral progressive exophthalmos. J. Clin. Endocrinol. 14:673, 1954.

Hogan, M. J., Thygeson, P., and Kimura, S. J.: Uses and abuses of adrenal steroids and corticotropin. Arch. Ophthalmol. 53:165, 1955.

Kimura, S. J., Hogan, M. J., and Thygeson, P.: Fuchs' syndrome of heterochromic cyclitis. Arch. Ophthalmol. 54:179, 1955.

Hogan, M. J., Thygeson, P., and Kimura, S. J.: Effects of prednisone and prednisolone in ocular inflammation. Trans. Am. Acad. Ophthalmol. Otolaryngol. 59:780, 1955.

Hogan, M. J.: Ocular toxoplasmosis. Clinical and laboratory diagnosis; evaluation of immunologic tests; treatment. Arch. Ophthalmol. 55:333, 1956.

Kimura, S. J., Carriker, F. R., and Hogan, M. J.: Retinal vasculitis with intraocular hemorrhage. Classification and results of special studies. Arch. Ophthalmol. 56:361, 1956.

Thygeson, P., Kimura, S. J., and Hogan M. J.: Observations on herpetic keratitis and keratoconjunctivitis. Arch. Ophthalmol. 56:375, 1956.

Hogan, M. J., Zweigart, P. A., and Lewis, A.: Persistence of *Toxoplasma gondii* in ocular tissues. 1. Am. J. Ophthalmol. 42:84, 1956.

Boyer, H. K., Suran, A. A., Hogan, M. J., and McEwen, W. K.: Increase of residual protein of bovine vitreous during growth of the eye. Arch. Ophthalmol. 56:861, 1956.

Hogan, M. J.: Postoperative iridocyclitis, postoperative infections after cataract. In Symposium: Postoperative cataract complications. Part 2. Trans. Am Acad. Ophthalmol. Otolaryngol., vol. 61, Jan.-Feb., 1957.

Hogan, M. J., Kimura, S. J., and Thygeson, P.: Uveitis in association with rheumatism. Arch. Ophthalmol. 57:400, 1957.

Hogan, M. J.: Keratoconjunctivitis. The clinical characteristics of the California epidemic, 1941-42. Am. J. Ophthalmol. 43:41, 1957.

———: Corneal transplantation in the treatment of herpetic disease of the cornea. Am. J. Ophthalmol. 43:147, 1957.

———: Uveitis par infection exogene. In Sedan, J. (ed.): Therapeutique Medical Oculaire, volume 2, chap. 5. Paris, Masson et Cie, 1957.

———: Evaluation of vision screening methods in industry. Arch. Industr. Health 16:93, 1957.

Thygeson, P., Kimura, S. J., and Hogan, M. J.: Observations on uveitis associated with viral disease. Trans. Am. Ophthalmol. Soc. 55:333, 1957.

Hogan, M. J., Kimura, S. J., Lewis, A., and Zweigart, P.: Early and delayed ocular manifestations of congenital toxoplasmosis. Trans. Am. Ophthalmol. Soc. 55:276, 1957.

Kimura, S. J., and Hogan, M. J.: Uveitis in children. In The Pediatrics Clinics of North America. Philadelphia, W. B. Saunders Co., 1958.

Boyer, H. K., Suran, A. A., Scott, K. G., Hogan, M. J., and McEwen, W. K.: Studies on simulated vitreous hemorrhages. 1. Rate of disappearance of radiochromium-tagged red cells. Arch. Ophthalmol. 59:232, 1958.

Boyer, H. K., Suran, A. A., Hogan, M. J., and McEwen, W. K.: Studies on simulated vitreous hemorrhages. 2. The effects of lytic enzymes, surface-active agents, and urea. Arch. Ophthalmol. 59:333, 1958.

Hogan, M. J.: Lamellar keratoplasty for herpes febrilis ulceration of the cornea. Am. J. Ophthalmol. 45:106, 1958.

Garron, L. K., Feeney, M., McEwen, W. K., and Hogan, M. J.: Electron microscopic studies of the human eye. 1. Preliminary investigations of the trabeculas. Am. J. Ophthalmol. 46:27, 1958.

Hogan, M. J., Zweigart, P., and Lewis, A.: Experimental ocular toxoplasmosis. 2. Arch. Ophthalmol. 60:448, 1958.

Hogan, M. J.: Ocular toxoplasmosis. The XIV Jackson Memorial Lecture. Trans. Am. Acad. Ophthalmol. Otolaryngol., vol. 62, Jan.-Feb., 1958; Am. J. Ophthalmol. 46:467, 1958.

Hogan, M. J., Zweigart, P. A., and Lewis, A.: Recovery of *Toxoplasma* from a human eye. Arch. Ophthalmol. 60:548, 1958.

Hogan, M. J.: Acquired toxoplasmosis. In Sorsby, A. (ed.): Systemic Ophthalmology, 2nd ed. London, Butterworth, 1958.

———: Congenital toxoplasmosis; Rubella and other virus diseases. In Sorsby, A. (ed.): Systemic Ophthalmology, 2nd ed. London, Butterworth, 1958.

Hogan, M. J., Kimura, S. J., and Thygeson, P.: Signs and symptoms of uveitis. 1. Anterior uveitis. Am. J. Ophthalmol. 47:155, 1959.

Kimura, S. J., Thygeson, P., and Hogan, M. J.: Signs and symptoms of uveitis. 2. Classification of the posterior manifestations of uveitis. Am. J. Ophthalmol. 47:171, 1959.

Garron, L. K., Hogan M. J., McEwen, W. K., Feeney, M. L., and Esperson, J.: Electron microscopy of ocular tissue. Arch. Ophthalmol. 61:647, 1959.

Hogan, M. J.: Granulomatous uveitis in man and experimental animals. Survey Ophthalmol. 4:225, 1959.

Hine, C. H., McEwen, W. K., Meyers, F. H., Mettier, S. R. Jr., Boyer, H. J., and Hogan, M. J.: Eye irritation from air pollution. APCA J. 10:17, 1960.

Hogan, M. J., and Goodner, E. K.: Surgical treatment of epithelial cysts of the anterior chamber. Arch. Ophthalmol. 64:150, 1960.

Thygeson, P., Hogan, M. J., and Kimura, S. J.: The unfavorable effect of topical steroid therapy on herpetic keratitis. Trans. Am. Ophthalmol. Soc. 58:245, 1960.

Hogan, M. J., Yoneda, C., and Feeney, M. L.: Morphology and culture of *Toxoplasma*. Arch. Ophthalmol. 64:655, 1960; Trans. Am. Ophthalmol. Soc. 58:167, 1960.

Spencer, W. H., and Hogan, M. J.: Ocular manifestations of Chediak-Higashi syndrome. Am. J. Ophthalmol. 50:1197, 1960.

Hogan, M. J.: The experts discuss toxoplasmosis. Arch. Ophthalmol. 65:178, 1961.

Hogan, M. J., Yoneda, C., and Zweigart, P. A.: Growth of *Toxoplasma* strains in tissue culture. Am. J. Ophthalmol. 51:920, 1961.

Kimura, S. J., Diaz-Bonnet, V., Okumoto, M., and Hogan, M. J.: The effect of corticosteroid hormones on experimental herpes simplex keratitis. Am. J. Ophthalmol. 51:946, 1961.

Feeney, M. L., and Hogan, M. J.: Electron microscopy of the human choroid. 1. Cells and supporting structures. Am. J. Ophthalmol. 51:185, 1961.

Hogan, M. J., and Feeney, M. L.: Electron microscopy of the human choroid. 2. The choroidal nerves. Am. J. Ophthalmol. 51:1072, 1961.

Hogan, M. J., and Feeney, M. L.: Electron microscopy of the human choroid. 3. The blood vessels. Am. J. Ophthalmol. 51:1084, 1961.

Hogan, M. J., and Kimura, S. J.: Cyclitis and peripheral choroiditis. Arch. Ophthalmol. 66:667, 1961.

Hogan, M. J.: How much training in research should be a part of graduate training? Trans. Am. Acad. Ophthalmol. Otolaryngol. 65:908, 1961.

Hogan, M. J.: Ocular toxoplasmosis in adult patients. Survey Ophthalmol. 6:835, 1961.

Hogan, M. J.: Ultrastructure of the choroid. Its role in the pathogenesis of chorioretinal diseases. Trans. Pac. Coast Otoophthalmol. Soc. 42:61, 1961.

Hogan, M. J., Diaz-Bonnet, V., Okumoto, M., and Kimura, S. J.: Experimental staphylococcic keratitis. Invest. Ophthalmol. 1:267, 1962.

Hogan, M. J., and Zimmerman, L. E. (eds.): Ophthalmic Pathology. An Atlas and Textbook, 2nd ed. Philadelphia, W. B. Saunders, 1962.

Hogan, M. J., and Feeney, M. L.: Ultrastructure of malignant melanomas of the choroid. Invest. Oph-

thalmol. 1:544, 1962.

Hogan, M. J.: Epidemiology of uveitis. Arch. Ophthalmol. 68:440, 1962.

———: Interviews on IDU. New management of herpetic keratitis. Highlights Ophthalmol. 5:145, 1962.

Aronson, S. B., Hogan, M. J., and Zweigart, P.: Homoimmune uveitis in the guinea pig. 1. General concepts of auto- and homoimmunity, methods and manifestations. Arch. Ophthalmol. 69:105, 1963.

———:Homoimmune uveitis in the guinea pig. 2. Clinical manifestations. Arch. Ophthalmol. 69:203, 1963.

———: Homoimmune uveitis in the guinea pig. 3. Histopathologic manifestations of the disease. Arch. Ophthalmol. 69:208, 1963.

———: Homoimmune uveitis in the guinea pig. 4. The normal guinea pig eye; concurrent ocular disease in the guinea pig. Arch. Ophthalmol. 69:370, 1963.

———: Homoimmune uveitis in the guinea pig. 5. The effect of adrenal corticosteroid. Arch. Ophthalmol. 69:379, 1963.

Hogan, M. J. (ed.): Medical and Surgical Management of Glaucoma. In International Ophthalmology Clinics. Boston, Little, Brown and Co., 1963.

Hogan, M. J., and Feeney, M. L.: The ultrastructure of the retinal blood vessels. 1. The large vessels. J. Ultrastruct. Res. 9:10, 1963.

———: The ultrastructure of the retinal blood vessels. 2. The small vessels. J. Ultrastruct. Res. 9:29, 1963.

———: The ultrastructure of the retinal blood vessels. 3. Vascular-glial relationships. J. Ultrastruct. Res. 9:47, 1963.

———: Remarks made on acceptance of the Proctor Medal Award, June 18, 1963. Invest. Ophthalmol. 2:409, 1963.

———: The vitreous, its structure, and relations to the ciliary body and retina. Proctor Gold Medal Award Lecture. Invest. Ophthalmol. 2:418, 1963.

Goodner, E. K., Hogan, M. J., Jawetz, E., and Kimura, S. J. (eds.): Ocular Pharmacology and Therapeutics and the Problems of Medical Management. F. A. Davis Company, 1963.

Hogan, M. J.: Choroidal hemanigoma. Brief pathology case reports. Arch. Ophthalmol. 71:69, 1964.

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PERIVASCULAR AND INTERVASCULAR RETICULAR FIBERS OF THE RETINA

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We are privileged to contribute to this edition of the JOURNAL dedicated to Michael Hogan whose outstanding original work has rightly earned him an honored place in the annals of ophthalmology in both its scientific and clinical aspects.

From evidence provided by silver-impregnated specimens, we know that an argyrophilic reticular membrane surrounds all the smaller vessels in the body, as demonstrated by Plenk[1] who quoted earlier references. He showed that the membrane consisted of a fine meshwork of fibers with coarser fibers extending into the surrounding tissue (Fig. 1). Both Volterra[2] and Plenk[1] believed this reticular net was situated within the basement membrane and probably formed by Rouget's cells or pericytes. Plenk was fully aware—long before the advent of electron microscopy—that pericytes are situated within the basement membrane; he described them as embedded in the ground substances of the vessel and correctly illustrated them in the capillary wall. He also suggested that they had a contractile function.[3] Huzella[4] believed that alterations in the elasticity of these reticular fibers were responsible for capillary contractility, whereas Plenk[1] felt they were probably responsible for keeping capillaries open; the validity of either view still remains unsubstantiated.

According to recent studies, the basement membrane consists predominantly of collagenous protein—not of mucopolysaccharides as once thought—with a relatively small glycoprotein component[5] arranged in an amorphous matrix, which at the periphery acquires a coarser texture of larger fibrils with a diameter of ~10 nm, a faint periodicity of 20 nm, and cross sections that appear circular or hollow, similar to those found around elastic fibers. Palade[6] previously demonstrated them in the outer layer of the basement membrane of myocardial vessels of the rat, and Majno[7] identified them as the ultrastructural component corresponding to the pericapillary sheath of Plenk.[1] Fawcett[8] also stated that these coarser fibrils were probably responsible for the perivascular argyrophilic network.

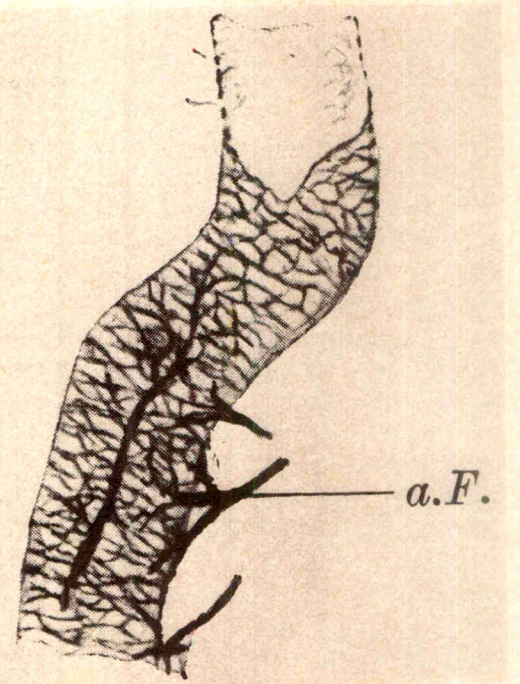


Fig. 1 (Ashton and Tripathi). A capillary of the thymus showing coarse reticular connective tissue fibers spreading around the capillary to form a delicate branching network. a.f. designates adventitial fibers. (From Plenk[1]).

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The cerebral vessels are particularly relevant to vessels in the retina and are likely to have a similar structure. As Bairati[9] pointed out, it has been known for some time that there is a perivascular connective tissue sheath extending from the pia mater into the depth of the neural tissue; how far it extends is difficult to determine. Schaltenbrand and Bailey[10] suggested that it ended in a terminal ring, whereas Patek[11] stated it became fenestrated and finally disappeared. According to Bairati,[9] this connective tissue membrane is covered by a glial layer composed of the feet of neuroglial cells that form dense interlacing fibrils. Whether the capillaries of the central nervous system are enveloped by an adventitial reticular layer was uncertain, but Bairati[9] maintained that such a layer, similar to that found around capillaries in other organs, was also present around the cerebral capillaries, although it tends to disappear from the precapillary to the true capillary. Capillaries in the mesencephalon, however, show typical "reticulated adventitia."

Perivascular reticular fibers in the retina—Maeda,[12] Hogan and Feeney,[13,14] Ishikawa,[15] and many others have described the ultrastructure of retinal vessels. The continuous lining of endothelial cells lies upon a homogeneous basal lamina, enclosing pericytes or muscle cells, that at the glial interface consists of two components, the basal lamina of the outermost vascular cell and the basal lamina of the investing glia. These may be separated by a dielectronic band, as noted by Hogan and Feeney[13,14] in the human fetal retina, and are probably a potential space separating ectodermal and mesodermal basal laminae. From the capillaries to larger vessels, these two layers gradually separate and coarser fibrils appear between them, providing the same structure in extraocular vessels, that is, an inner homogeneous basal lamina and an outer fibrillar coat (alternatively referred to as the adventitia) (Fig. 2). In the largest vessels nearer the optic nerve head and within the nerve itself, this perivascular space enlarges still further and contains conventional collagenous connective tissue.[16]

By light microscopy, does the argyrophilic network of Plenk exist around the retinal vessels, and, if so, to what does it correspond ultrastructurally? It is not mentioned as such in the standard textbooks of Parsons,[17] Salzmann,[18] Wolff,[19] or in the classic works of Müller[20] and Leber[21] or in the recent review by Cogan and Kuwabara.[22] Duke-Elder,[23] however, stated that as the retinal vessels develop they "are clothed with a glial sheath derived from the cone itself." Krückmann[24,25] described the only perivascular membrane in the adult retina, termed it "membrane limitans perivascularis," and considered it to be formed by glia; this is often referred to as Krückmann's membrane. This membrane, however, was demonstrated in sections and was never described as composed of argyrophilic fibers. When one studies his diagrams today with a knowledge of retinal ultrastructure, it seems that he was describing the adjacent walls of Müller glial cells or astroglial cells that surround the vessels and abut directly on the basement membrane.

Wolter,[26–29] in his various studies of silver impregnation in the retina, demonstrated an argyrophilic perivascular network that was composed of a special type of neuroglia that proliferates in senescence and chronic disease of the retina. In demonstrating this membrane in digest preparations, one of us (N.A.)[30,31] accepted this description and referred to it as the "pericapillary glial membrane" and presumed it was identical with Krückmann's membrane. Duke-Elder and Wybar[32] also gave this interpretation in their textbook of the anatomy of the eye. Hogan, Alvarado, and Weddell[33] described a specialized

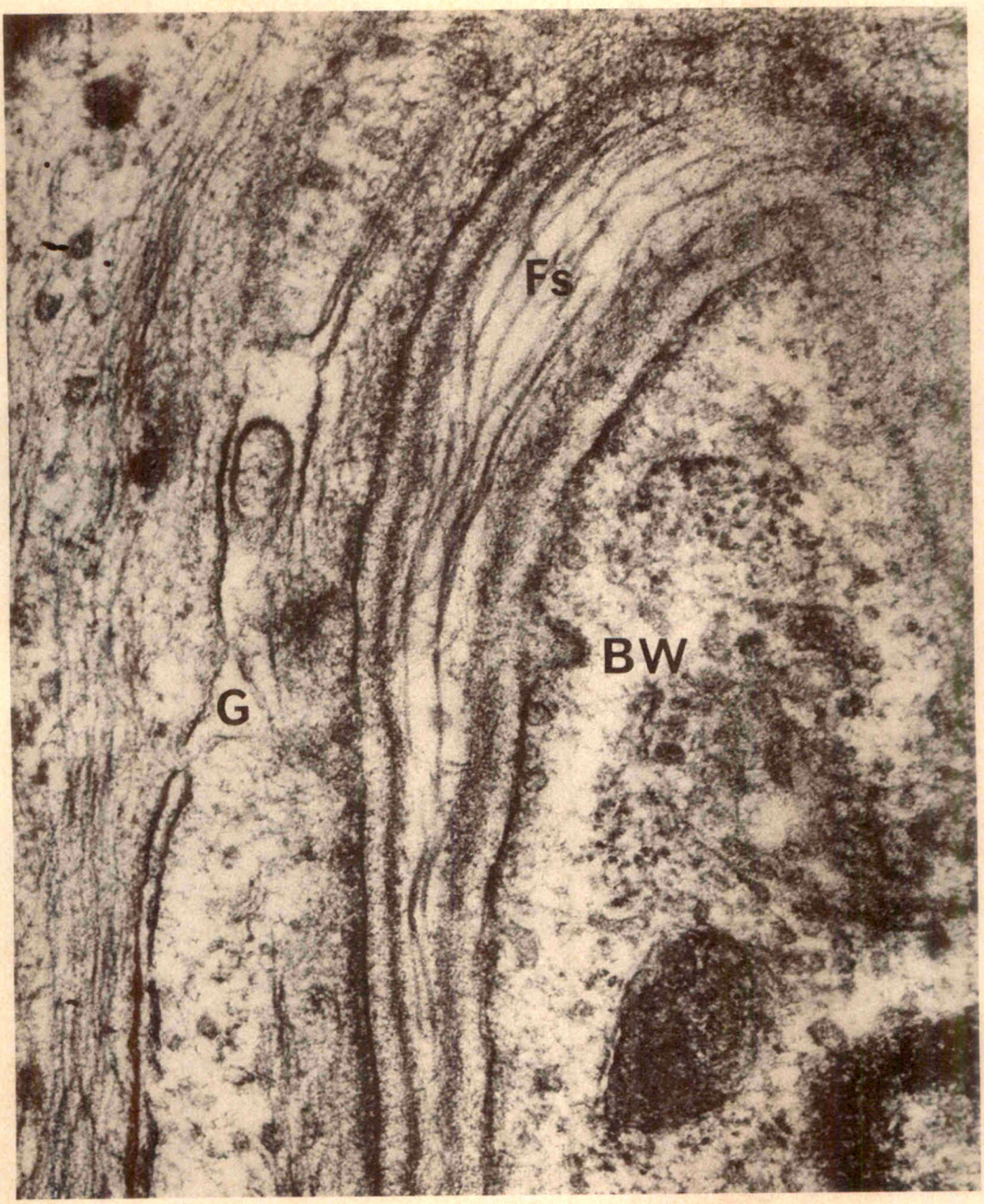


Fig. 2 (Ashton and Tripathi). A retinal vessel of a baby rabbit showing the appearance of fine fibrils (Fs) in the electronlucent space developing between the basal laminae of the mesodermally derived blood vessel wall (BW) and the neuroectodermally derived surrounding glia (G). Note the obliteration of this space in some regions (osmium tetroxide fixed; uranyl acetate/lead citrate, ×70,000).

system of perivascular glia as originally reported by Liss[34] in the central nervous system.

Recent studies in our laboratory showed, when sections of the retina were stained by Wilder's silver impregnation method or Gomori's stain for reticulin, an argyrophilic perivascular network selectively stained against the unstained nervous tissue (Fig. 3); in digest preparations stained in a similar way, the pattern of the network is more apparent and can be seen investing arteries, veins, and capillaries in the same manner seen in extraocular vessels (Fig. 4). These findings, with the recognition of the likelihood of previous misinterpretations in the nature of the network, were presented by one of us (N.A.) in a presidential address before the Ophthalmological Section of the Royal Society of Medicine Oct. 14, 1971 (unpublished data). However, Daicker[35,36] described in detail the normal and pathologic appearances, by light microscopy, of this retinal argyrophilic fiber network, in its perivascular and extravascular situations and in disease conditions. We compare his light microscopic studies with our own and report our electron microscopic studies of these structures.

Material and methods

We obtained evidence from three main sources: sections and retinal digests stained by silver reticulin methods; enzymatic studies on retinal digests; and electron microscopy.

Sections and digests—Routine celloidin sections of human eyes of various ages enucleated for malignant melanoma

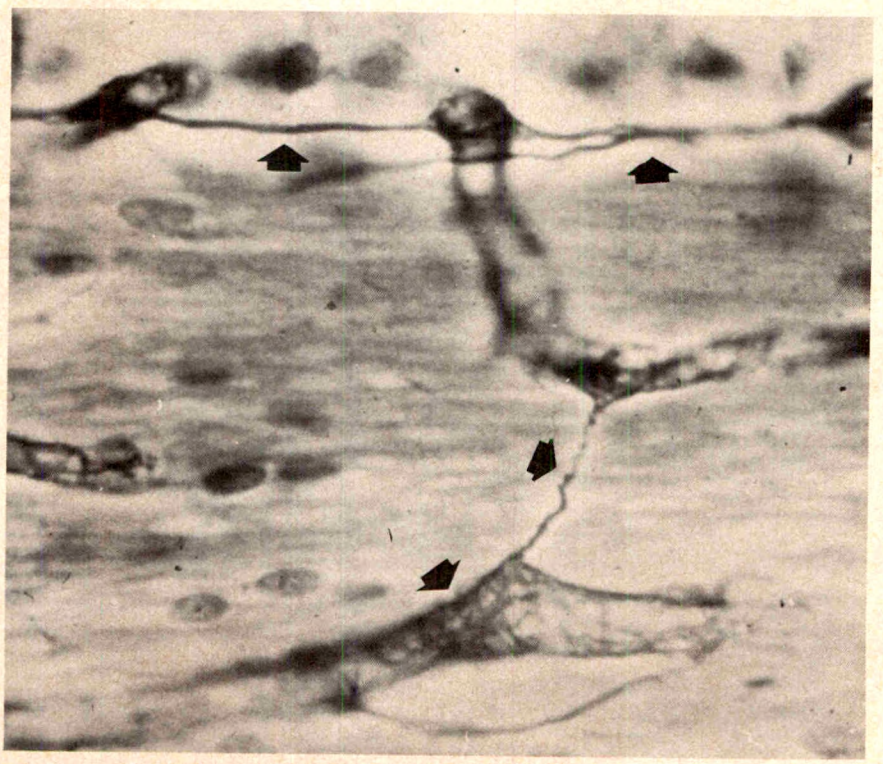


Fig. 3 (Ashton and Tripathi). Section of human retina (disk region) showing argyrophilic fibers forming pericapillary networks (arrows) and interconnecting strands. The surrounding nervous tissue is relatively unstained (Wilder's reticulin stain, ×1,200).

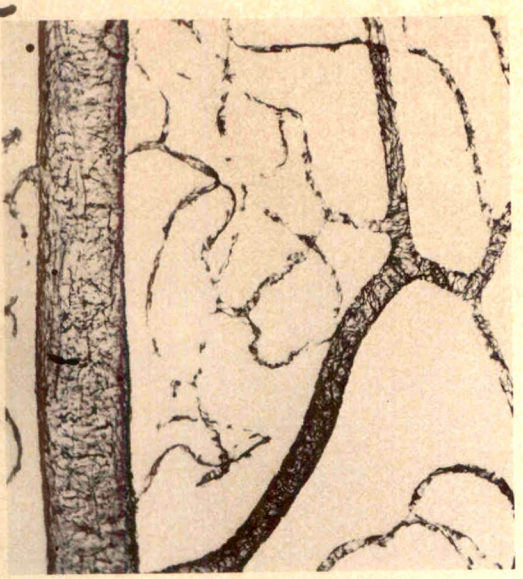


Fig. 4 (Ashton and Tripathi). Human retinal vessels. The argyrophilic network surrounds all vessels, but becomes patchy and attenuated in the capillaries (digest preparation; Wilder's reticulin stain, ×120).

of the choroid were used. Retinal digests of human, monkey, cat, kitten, rabbit, and human diabetic retinas were stained by either Wilder's or Gomori's reticulin method.

Enzymatic studies—REAGENTS—We used pepsin, 3% in 1% hydrochloric acid at pH 1.5; trypsin, 3% in Tris buffer at pH 7.8; and collagenase, 0.1% in basic salt solution containing 1,000 units of penicillin/ml at pH 7.0.

EXPERIMENTS ALL ON HUMAN RETINAS—Pieces of retina, fixed in 10% formaldehyde saline, were incubated in pepsin solution at 37°C for 20 minutes to 17½ hours followed by trypsin solution at 37°C, if required for complete digestion, and stained (Gomori's). Pieces of unfixed postmortem retinas were digested in trypsin solution, washed in basic salt solution, incubated in collagenase solution at 37°C for four hours, fixed in 10% formaldehyde saline, and stained (Gomori's). Pieces of postmortem retinas, fixed in Carnoy's fluid for either 20 minutes or two hours, were washed in basic salt solution, incubated in collagenase solution for five hours at 37°C, fixed in formaldehyde saline, and digested in trypsin according to the method of Kuwabara and Cogan[37] and stained (Gomori's).

All specimens were compared with controls taken from the same retinas, fixed in 10% formaldehyde saline, digested with trypsin, and stained (Gomori's).

Electron microscopy—We examined pieces of tissue from various regions of normal and diseased human retinas (including diabetic), obtained from eyes enucleated at operation for malignant disease involving the orbit or from eyes enucleated for small choroidal melanoma, and normal retinas from monkey eyes. The specimens were fixed for two to four hours in isotonic glutaraldehyde (2.5% solution in sodium cacodylate buffer at pH 7.4), dehydrated, and embedded in epoxy resin (Araldite). Ultrathin sections (40 to 80 nm) were cut by using glass knives and floated on distilled water baths. For routine electron microscopy, sections were stained with uranyl acetate followed by lead citrate. For the periodic acid silver methenamine staining technique, ultrathin sections were floated on 2% periodic acid solution at room temperature for 20 minutes. The sections were then rinsed in at least four changes of distilled water and left in the last bath for 30 to 60 minutes. Sections were then transferred onto a bath of freshly prepared silver methenamine (2 ml of 5% silver nitrate added, drop by drop, to 18 ml of hexamine followed by 2 ml of 2% sodium borate solution in distilled water), and incubated in the dark at 60 to 70°C. After approximately 50 minutes, the sections were briefly examined in the light and, as soon as a pale brown color was observed, transferred to a distilled water bath. After several rinses in distilled water, the last for more than one hour, the sections were floated for five minutes on 3% sodium thiosulphate and rapidly

rinsed again in distilled water. The sections were then examined by electron microscopy.

To resolve the problem of the structural basis of the argyrophilic reticular network seen by light microscopy, various specimens of human, monkey, and kitten retinas were fixed in 10% formaldehyde saline or 3% glutaraldehyde, digested by the trypsin method,[37] and stained by Gomori's silver reticulin method. Vessels exhibiting the reticulin pattern were selected, postfixed in 1% osmium tetroxide, dehydrated and embedded in epoxy resin. Additionally, pieces of retinas fixed either in 10% formaldehyde saline or 3% glutaraldehyde were stained for reticulin (Gomori's), postfixed in osmium tetroxide, and processed for electron microscopy. Semithin sections, unstained or stained with toluidine blue, were examined by light microscopy and ultrathin sections, with and without uranyl acetate and lead citrate staining, were examined by electron microscopy.

Discussion

Pattern of network—Our findings in digest preparations stained by Wilder or Gomori's technique for reticulin closely correspond to Daicker's findings,[35] using Gomori's method, especially in his general description of the pattern and extent of a perivascular argyrophilic network spreading continuously around the arterioles, precapillary arterioles, postcapillary venules, and venules of the human retina gradually becoming attenuated, patchy, or absent around the capillaries. We demonstrated this network in the retinas of man, monkeys, cats, kittens, and rabbits (Figs. 4-7).

We agree with Daicker who described the distinctive patterns between these different vessels. He found that a definite argyrophilic fiber system did not become apparent until the second order of branching of the large vessels from the disk. Such fibers, however, were identified tinctorially and enzymatically (resistance to trypsin and digestion by collagenase) by Daicker as collagen fibers, agreeing with the electron microscopic studies of Anderson and Hoyt.[16]

The pattern of the network around small arterioles differed from that around venules. In arterioles, the network was markedly wavy and mostly circular, with fibers of varying thickness that branched and anastomosed with each other and extended directly onto their branch vessels (Fig. 5). The network diminished toward the periphery, although we stress that argyrophilic fibers in older people are most pronounced at the periphery where they may form dense branches throughout the retina. In venules, the interlacing fibers tended to run in the long axis of the vessel, branching in arcades and showing perpendicular fibers; occasionally, there were longitudinal fibers external to this network. This sheath of fibers, as in the case of the arterioles, extended onto the smaller venous branches, although the fibers are coarser (Fig. 6). Adventitial argyrophilic fibers, especially from smaller venular branches, often stretched out freely into the intervascular spaces. At arteriovenous crossings, Daicker[35] found the network shared by the adjacent vessels. Capillaries were generally free from argyrophilic fibers except for isolated areas and interconnecting argyrophilic strands, that were not related to pericytes (Fig. 7). There are dangers of artifact in digest preparations, however, especially when there are free-ended fibers or fibers unrelated to vessels, since this disruptive process can grossly distort normal anatomic relationships.

Significance of argyrophilia—Silver staining is a notoriously capricious histologic technique for identifying the nature or chemical composition of positively staining structures because the property is shared by many heterogenous sub-

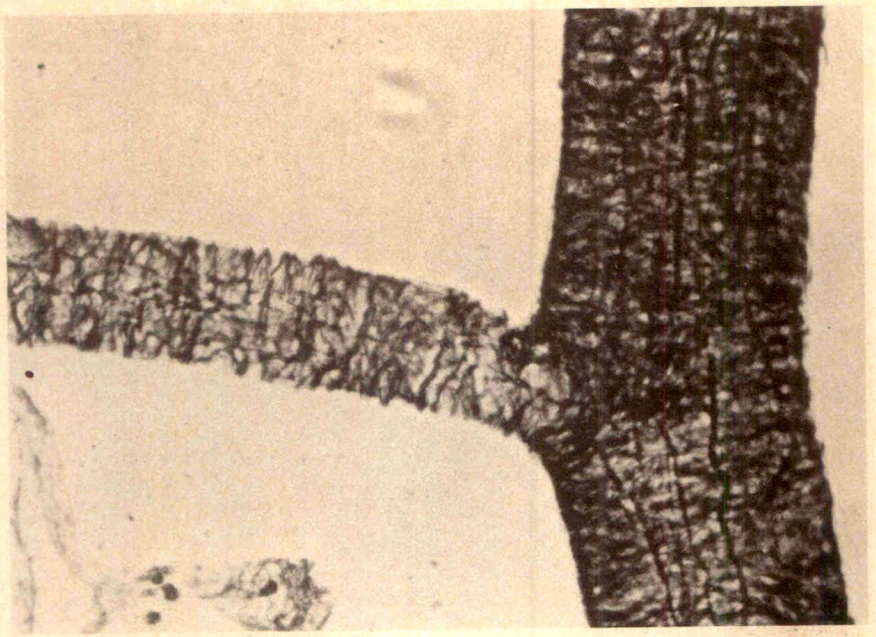


Fig. 5 (Ashton and Tripathi). Human retinal arteriole. The branch vessel shows an encircling perivascular argyrophilic network consisting of wavy fibers continuous with those of the main trunk (digest preparation; Gomori's reticulin stain; phase contrast, ×360).

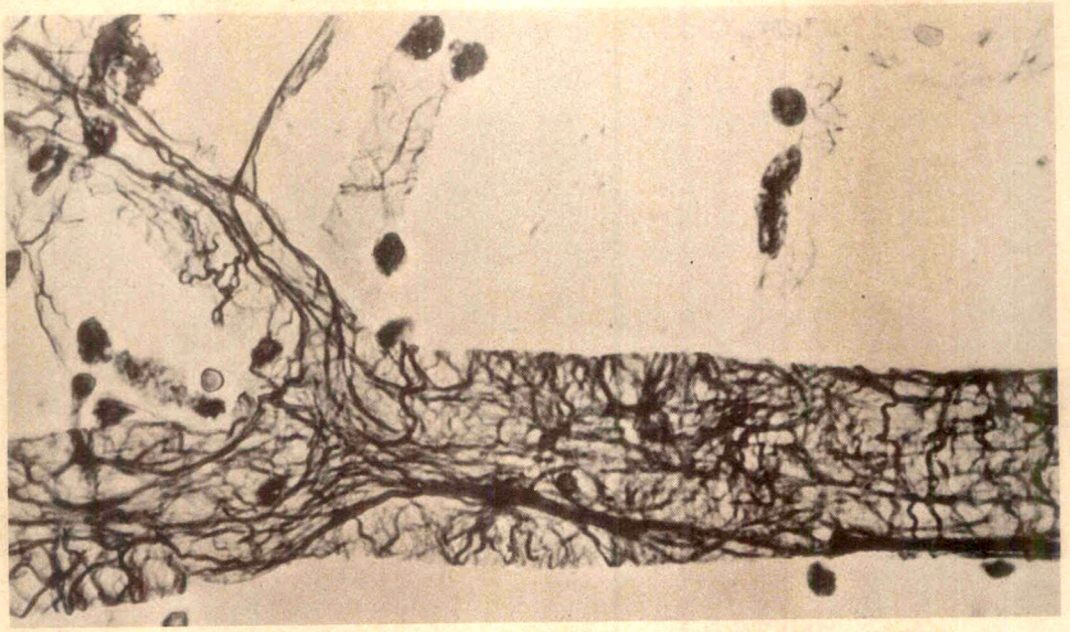


Fig. 6 (Ashton and Tripathi). Human retinal venule. The interlacing argyrophilic fibers tend to run in the long axis of the vessel. Coarser longitudinal fibers, lying more externally, extend into the branch vessel (digest preparation; Gomori's reticulin stain; phase contrast, ×290).

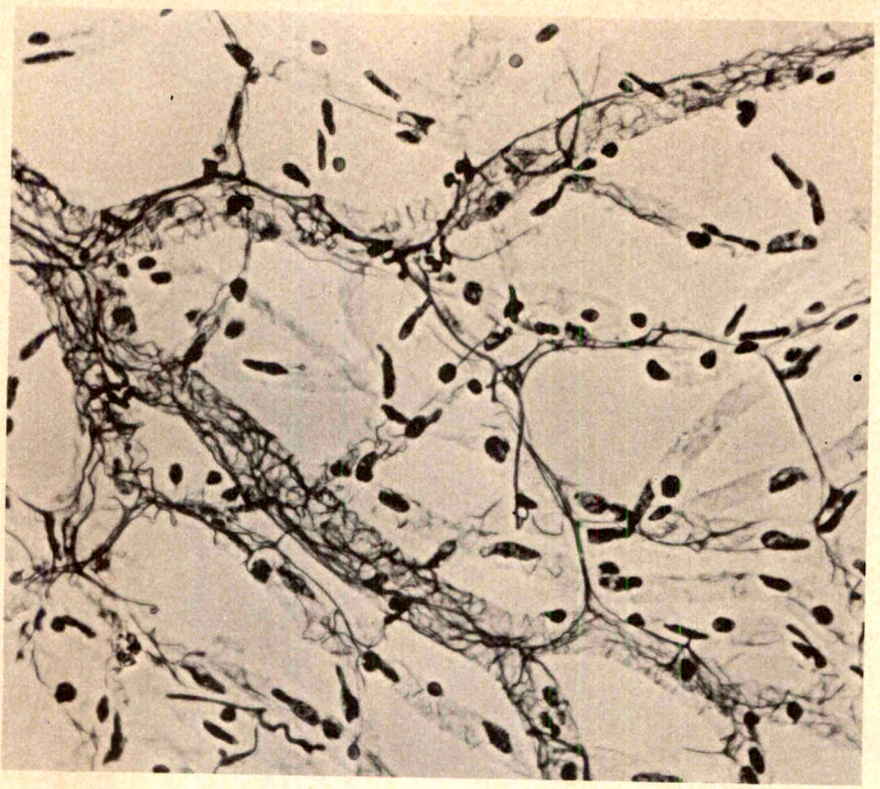


Fig. 7 (Ashton and Tripathi). Human retinal digest showing capillaries and postcapillary venules. Note that whereas the larger vessels show a dense plexus of argyrophilic fibers, the network of the capillaries is patchy and often absent. Several intercapillary strands may also be seen (Gomori's reticulin stain; phase contrast, ×360).

stances, as in the argentaffin reactions of melanin, enterochromaffin, lipofuscins, metals, glycogen, mucin, fungi, and nucleic acids, and the argyrophilic reactions of neuroglia, axons, degenerating axons,[38] nerve cells, and reticular fibers, differing structures which can sometimes be selectively stained by varying the technical procedure. Nevertheless, known and unknown factors in fixation and staining can lead to confusing results, even in tissues from the same species of animal,[39] and this is especially confusing in differentiating collagenous from neural tissue.

It is not appropriate to discuss this complex subject[38–42] but Pearse[43] commented, "When any of the numerous silver techniques for reticulin are used, many of the fibers which are stained are certainly fine nerve fibers." In short, it is not always possible to ascertain whether argyrophilic fibers are nervous or mesodermal in origin.

Using the silver carbonate methods of Rio Hortega, various argyrophilic structures and networks in the retina have been described as proliferating perivascular glia,[26,27] degenerated and hyalinized astroglia,[44] perivascular astroglia,[26,28,29,45,46] fibrous strands in retinoblastoma,[47] pericytes,[48] and interwoven nerve fibers related to retinal vessels.[49] Since many of our figures resemble the argyrophilic perivascular network and intervascular strands desribed by Daicker[35,36] as reticulin, supportive evidence other than argyrophilia must be presented before this conclusion is justified, or dif-

ferent kinds of argyrophilic perivascular fibers must be demonstrated.

Enzyme studies—As regards the particular structures we are describing, we believe Daicker's[35] findings—particularly selective enzymatic digestion (resistance to trypsin and digestion by collagenase)—would, if supported by others, establish the existence of reticulin as at least one perivascular entity.

However, it is difficult to assess the influence of enzyme action because of variability in staining of the network in control retinas. The factors involved are complex, such as the methods and periods of fixation, differences in the rate of digestion, postmortem age of the retinas before fixation, and so on, and there are no reliable standards.

While our enzyme studies confirmed that the fibers are resistant to trypsin since they normally persist after routine digestion, we obtained such variable results with pepsin (20 to 30 minutes, two, six, seven, and 17½ hours) and collagenase (four and five hours), both of which should digest reticulin, and found that many argyrophilic fibers of the perivascular network persisted even after the longest exposure, that we cannot claim to have duplicated Daicker's[35] findings.

Intercapillary connections—In retinal digests, two forms of intercapillary connections, or "bridges" as they were originally named by Kuwabara and Cogan,[37] are identifiable. The first is an attenuated degenerate capillary, usually acellular and sometimes referred to as a "dead capillary" (Fig. 8); the other is a delicate interconnecting strand, recently referred

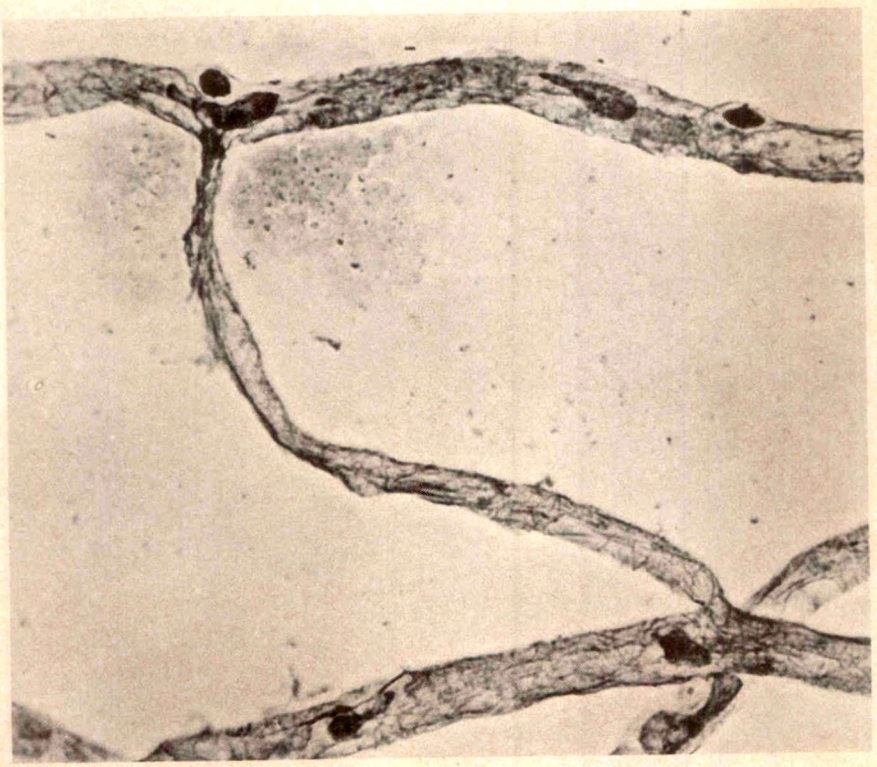


Fig. 8 (Ashton and Tripathi). Human retinal digest showing an intercapillary connection formed by an attenuated dead capillary (Gomori's reticulin stain; phase contrast, ×720).

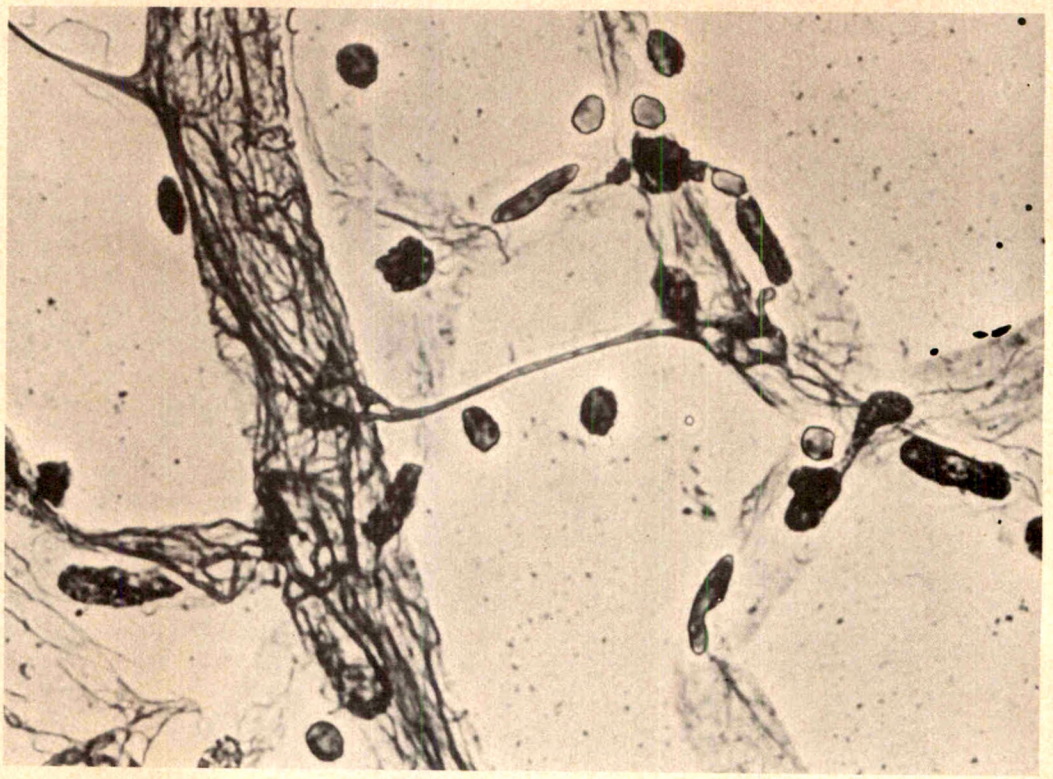


Fig. 9 (Ashton and Tripathi). Human retinal digest preparation showing an intercapillary connection formed by an argyrophilic fiber continuous with perivascular reticulin network (Gomori's reticulin stain; phase contrast, ×900)

to by Daicker[35] as a "mesodermal strand" (Fig. 9). Both connections were illustrated by Kuwabara and Cogan,[37] Ashton,[30] and Kuwabara, Carroll, and Cogan.[50] These structures have been recognized in other tissues for many years.[51] It has been postulated that both retinal structures represent either retracted capillaries as part of the process of retinal angiogenesis, or atrophic capillaries in aging, or degenerative conditions.[30,51]

While the intercapillary bridge derived from a closed capillary and consisting solely of acellular basement membrane is now a generally accepted entity, Daicker[35,36] advanced the view that the mesodermal strand, based on its positive staining for reticulin and its clear continuance with the perivascular reticular fiber network, is a distinct and separate entity of unknown origin. Its argyrophilia contrasts strongly with the negative silver staining of the basement membrane bridges, and we believe his distinction between the two types of intercapillary connections is correct. According to Daicker,[35,36] both the reticular fiber network and the mesodermal strands are insensitive to trypsin and digested by collagenase, indicating that they consist of collagenous protein and that an origin from nervous tissue can be excluded. Unfortunately, we have not been able to demonstrate digestion with collagenase (or pepsin) consistently to support his conclusions, although there are other reasons for regarding this view as correct.

Relationship to vascularization—If, despite this inconclusive evidence, these argyrophilic pericapillary and intercapillary fibers are regarded as mesodermal, then they are probably related to the vas-

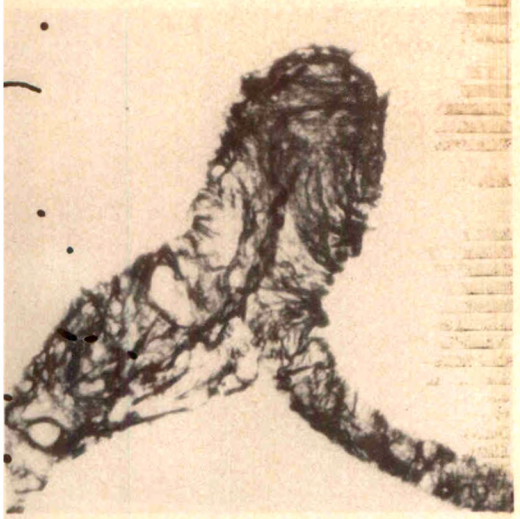


Fig. 11 (Ashton and Tripathi). Human diabetic retina showing coarse argyrophilic fibers encircling a loop aneurysm (digest preparation; Wilder's reticulin stain, ×500).

Gomori's silver reticulin stain, and retinal digests similarly stained and submitted to electron microscopy by selecting vessels showing the network, the argyrophilic fibers corresponded exactly to the fibers normally found in this perivascular location at the glial and vessel interface.

In pathologic conditions (for example, diabetic retinopathy), there were many fibrils in the vessel-glial interspace of the larger vessels, in the basal lamina enclosing muscle cells (Fig. 18), and occasionally in the basal lamina of the vascular endothelial lining.

In sections stained with uranyl acetate and lead citrate, the fibrils of the vascular sheath exhibited an electron density similar to the basal lamina material. The fibrils were of indeterminate length, and approximately 24 nm thick. In suitably orientated fibrils, we saw a faint repeating periodicity of 16.5 nm along their long axes (Fig. 19, top). Thus these fibrils could be differentiated from the mature regular collagen fibrils normally found in the adventitial sheath of larger retinal vessels and also in the medium vessels of senile and pathologic retinas. Although, in morphology and staining reaction, the fine fibrils of the vascular sheath closely approximated those of the collagenous fibrils of the vitreous cavity (Fig. 19, bottom), the diameter of the vitreous fibrils appeared to be smaller.

In sections stained with silver methenamine, the fibrils contrasted well with the basal lamina material and also with the surrounding glial tissue (Fig. 20). This differential staining, however, became less obvious in sections exposed for longer periods of time to silver methenamine. The argyrophilia of these fibrils seemed strong and independent of the method of fixation since tissues fixed primarily in formaldehyde saline or osmium tetroxide did not alter the staining reaction. We obtained similar results in ultrathin sections stained with silver methenamine without prior treatment with periodic acid (Fig. 17). This unexplained behavior of silver staining poses a problem in the interpretation of the results obtained.

Proliferating glia invading the lumen of degenerate vessels was not argyrophilic to silver methenamine, whereas the proliferating perivascular fibers stained intensely, suggesting that they are not of glial origin (Fig. 21).

Nature of the perivascular network—We conclude that the perivascular network of the retina and intercapillary strands is probably composed of reticulin

Fig. 10 (Ashton and Tripathi). Kitten retinal digests showing developing retinal vessels. Retracting capillary (thin arrows) and argyrophilic intercapillary strands (wide arrows) are evident. Top, The strands are continuous with an argyrophilic perivascular network. Center, There is a clear relationship between retracting capillary and intercapillary strands. Bottom, There are many argyrophilic fibers apparently not related to the vessels except through occasional connections. These may represent the reamnants of the primitive vasoformative tissue (Wilder's reticulin stain, ×390).



Fig. 12 (Ashton and Tripathi). Human diabetic retina showing Y-shaped capillaries bound together by argyrophilic fibers. No fibers are seen on the closed capillaries with which they connect (digest preparation; Wilder's reticulin stain, ×450).

for the following reasons. The fibers are stained by silver methods said to be specific for reticulin and, in sections, the surrounding neural tissue does not stain by these methods; moreover, glial tissue invading a vessel lumen is not argyrophilic. The pattern of the network around the vessels is identical with that visible throughout the body, including the central nervous system, suggesting that Müller fibers are not involved in its formation. The collagenous nature of the argyrophilic fibers is indicated by their resistance to trypsin and, according to Daicker,[35] their sensitivity to collagenase (not found in our studies). Ultrastructurally, the network is situated between the basement membranes of the vascular and neural tissue, that is, it is structurally related, like reticulin, to basement membrane and not to nervous elements (Fig.



Fig. 13 (Ashton and Tripathi). Human retinal digest showing senile changes at the periphery consisting of a tangled mass of coarse perivascular and intervascular argyrophilic fibers (Gomori's reticulin stain, ×360).

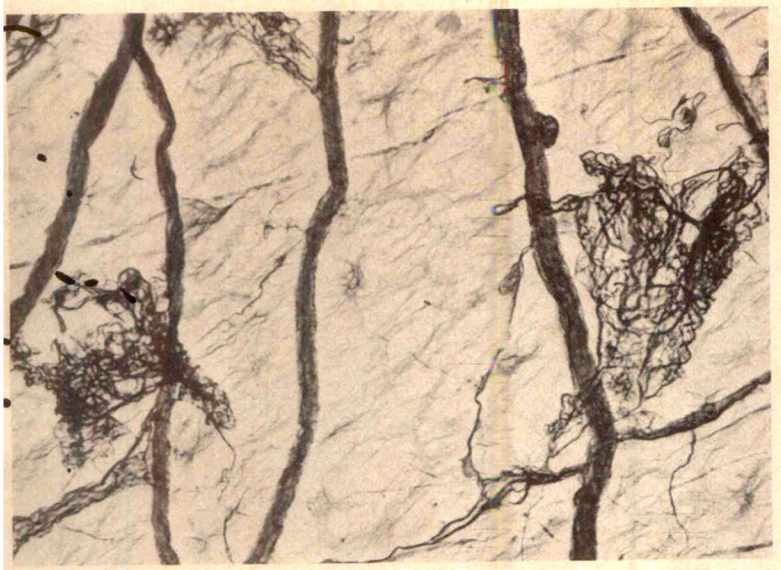


Fig. 14 (Ashton and Tripathi). Human diabetic retina showing strands and tangled masses of argyrophilic fibers. In the background the inner limiting membrane is adherent; hence, the fibers may not be intraretinal in origin and their true nature is unknown (digest preparation; Wilder's reticulin stain, ×180).

22). It consists of fine fibrils, has an affinity for silver methenamine, and shows indefinite periodic banding of approximately 16 nm. They are clearly not neuronal fibers, but probably belong to the collagenous group of fibers of which reticulin is thought to be an example. Reticulin, however, is essentially an entity of light microscopy and its exact ultrastructure has not been fully identified. Vitreous fibrils adjacent to the inner limiting membranes were also argyrophilic and morphologically similar to, although finer than, the perivascular fibers.

If this network was not reticulin and corresponded to the "perivascular glia" described by Wolter[26-29] and Hogan, Alvarado, and Weddell,[33] we could only attribute it to the glial cells that exist within the retina. Reasons have already been given why this network is probably not due to Müller fibers but, owing to the vagaries of argyrophilia and the uncertainties of enzyme digestion, the presence of an astrocytic network cannot be excluded. This seems unlikely since such a network would be expected to be digested by trypsin; however, there is a possibility that a neural fiber network may exist in addition to a reticulin network.

This question must to some extent remain an open one since neither argyrophilia, enzymatic digestion, nor electron microscopy have provided irrefutable evidence to establish the reticulin nature of the network. Pras and Glynn[56] recently extracted from reticulin a new noncollagenous protein, soluble in distilled water, whose antibodies showed specific antireticulin staining by immunofluorescent techniques. This new finding may be valuable in resolving our present doubts and may better demonstrate the distribution of reticulin in the retina and establish, in conjunction with the other methods, whether any kind of perivascular glial network is or is not an entity.

SUMMARY

We demonstrated the existence in the retina of an argyrophilic perivascular membrane comparable in all respects to that which exists throughout the vascular system. We compared our findings by light microscopy with those previously reported. We identified, by electron microscopy, the normal general location of the network between the basal laminae of the glial and vessel cells and demonstrated its selective staining with silver methe-

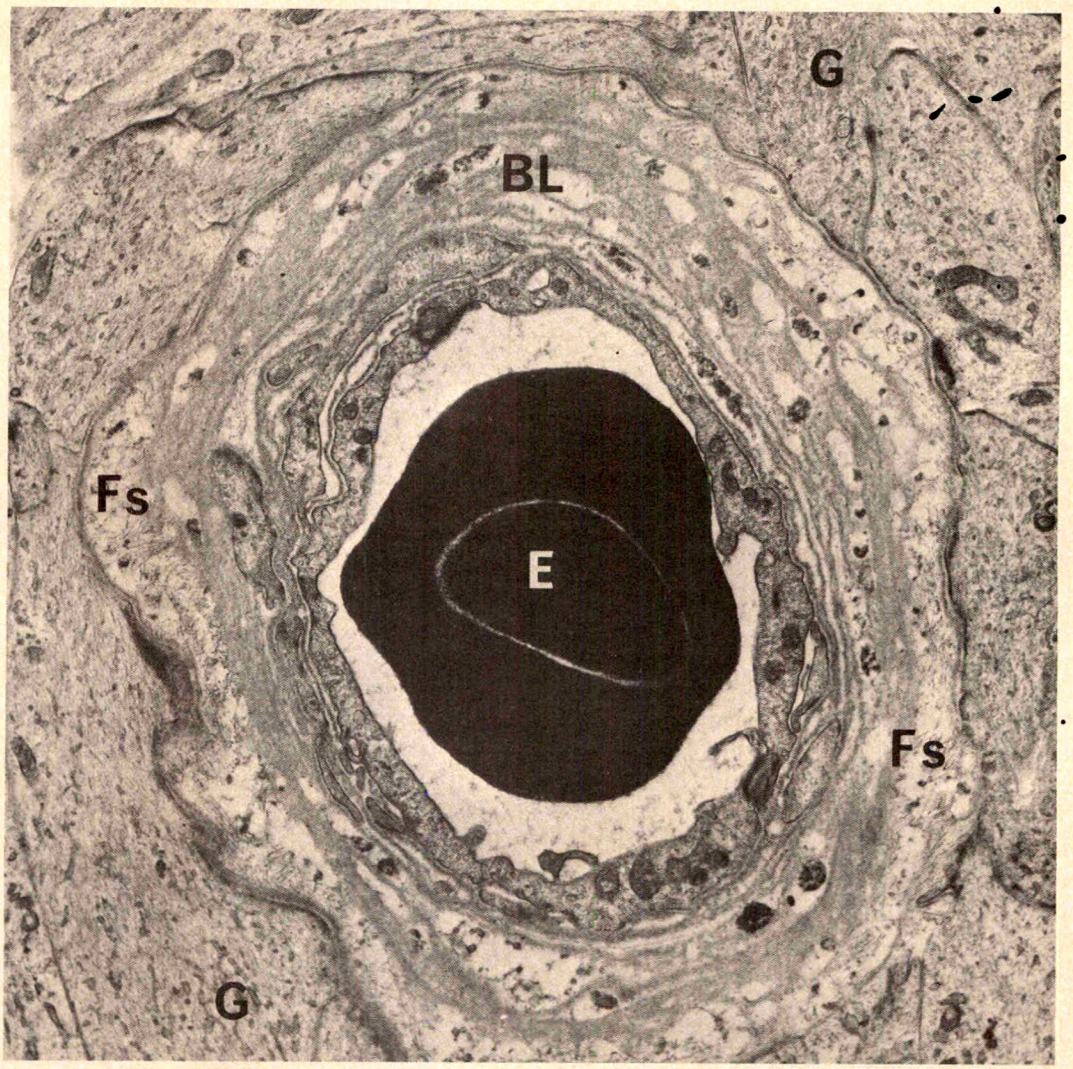


Fig. 15 (Ashton and Tripathi). A small retinal vessel in an aging human eye. Note the presence of fine fibrils (Fs) between the basal laminae of the glial cells (G) and the thickened cavitated basal lamina (BL) of the vessel; E indicates erythrocyte in the vessel lumen (osmium tetroxide fixed; uranyl acetate/lead citrate, ×10,500).

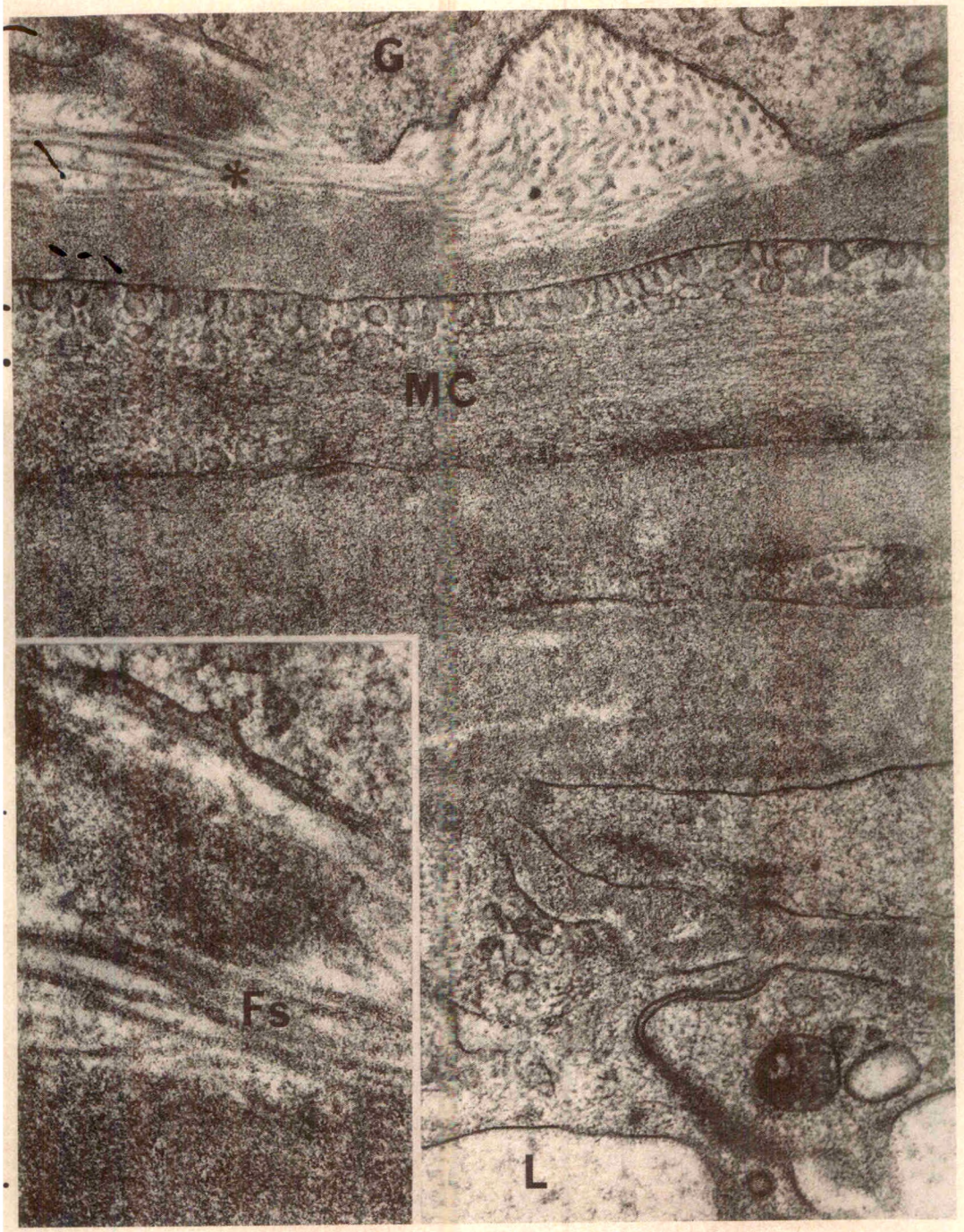


Fig. 16 (Ashton and Tripathi). The wall of a precapillary arteriole in a normal human retina showing the location of fine fibrils (asterisk) between the basal laminae of the perivascular glial cells (G) and arteriole (×75,000). Insert corresponds to the area marked with an asterisk and shows the fibrils (Fs) and the surrounding basal lamina at higher magnification; MC indicates muscle cell of the arteriole; L, vessel lumen (osmium tetroxide fixed; uranyl acetate/lead citrate, ×114,000).

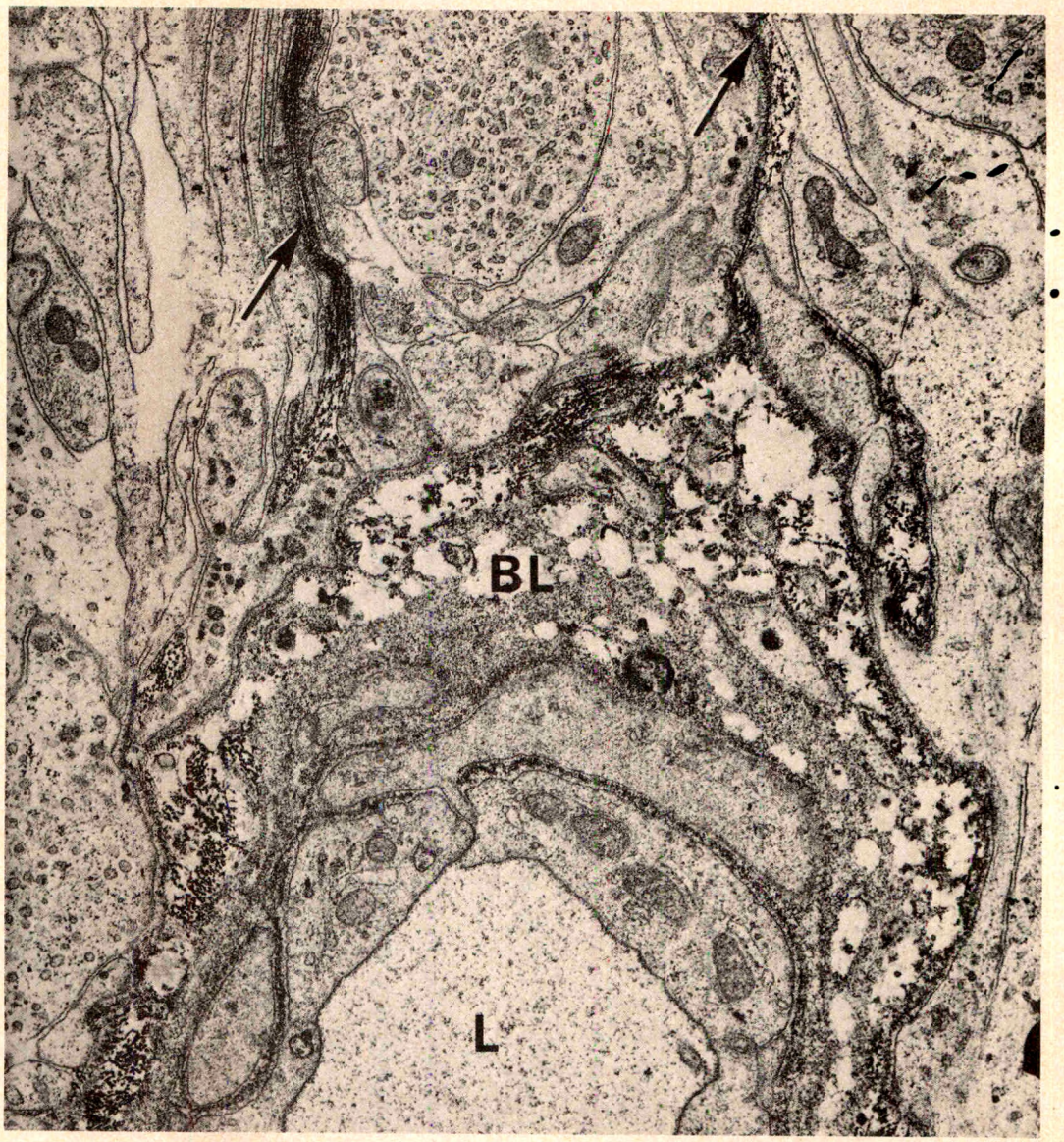


Fig. 17 (Ashton and Tripathi). A retinal vessel in a senile human eye. Arrows denote the extension of argyrophilic fine fibrils into the surrounding retina; L indicates lumen of the vessel; BL, basal lamina showing cavitations and fine argyrophilic fibrils. Note specific affinity of the fibrils for the silver (osmium tetroxide fixed; ultrathin sections stained with silver methenamine without prior treatment with periodic acid, ×18,500).

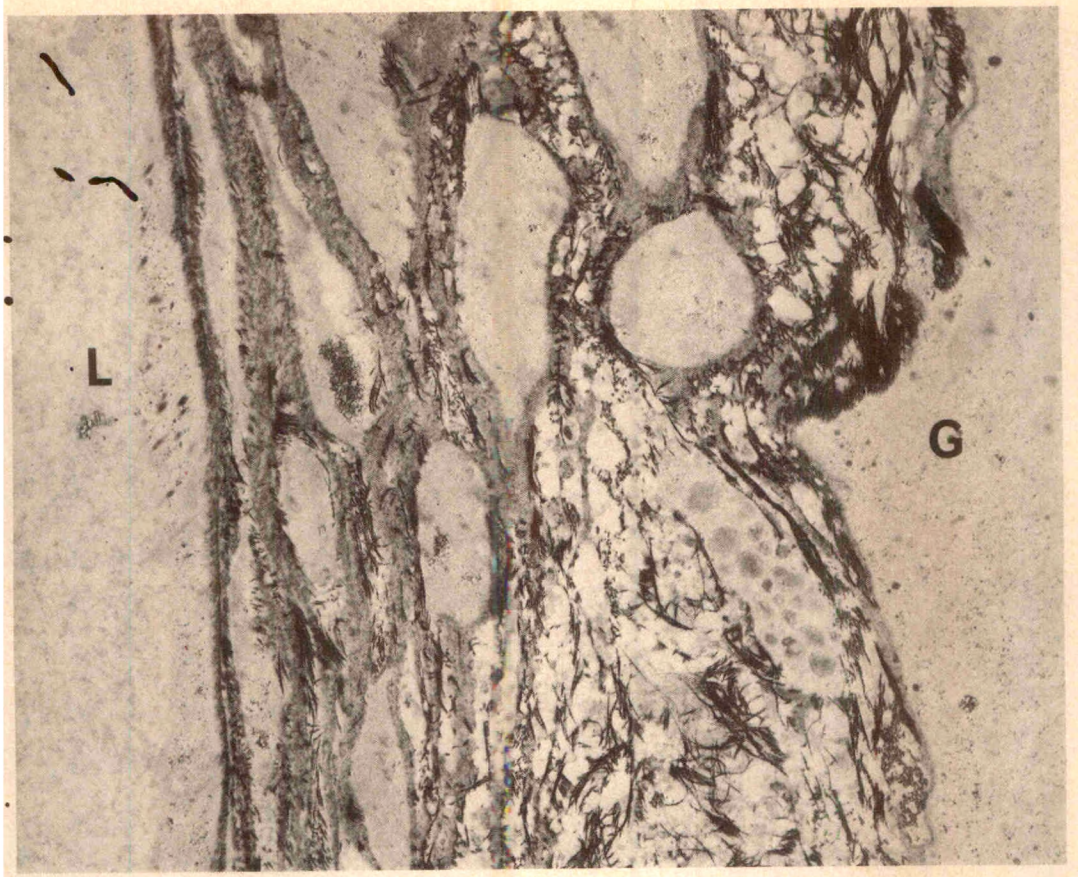


Fig. 18 (Ashton and Tripathi). A retinal vessel from a human diabetic showing abundance of argyrophilic fine fibrils in almost all layers of the basal laminae; L indicates lumen of the vessel; G, surrounding glial cells (glutaraldehyde/osmium tetroxide fixed; stained with silver methenamine after periodic acid treatment, ×8,000).

namine. These perivascular fibers, intercapillary strands, and bridges develop in relation to the process of retinal vascularization and the potential for forming these fibers is reactivated in senility and disease, as in diabetes. We summarized the evidence by concluding that these fibers are most likely composed of reticulin; it appears provable that in the past there may have been some confusion with neural fibers.

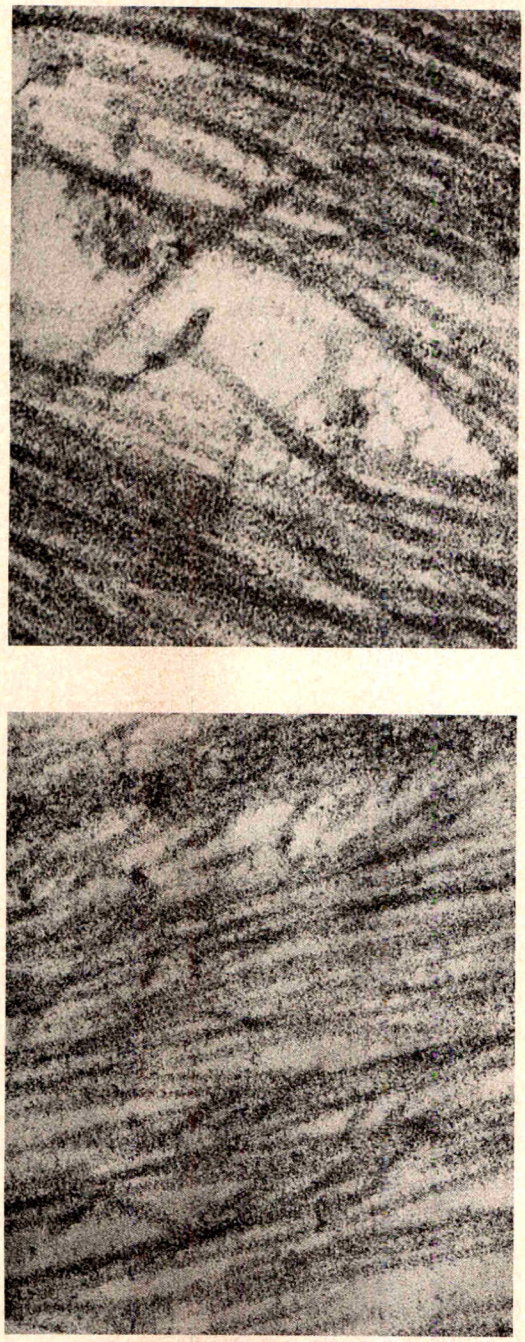


Fig. 19 (Ashton and Tripathi). Top, Electron micrograph of fine fibrils associated with the basal lamina of the vessel wall. Note the diameter (approximately 24 nm) and periodicity (approximately 16.5 nm) of the fibrils. Bottom, Compare the finer fibrils of the vitreous (osmium tetroxide fixed, uranyl acetate/lead citrate, ×105,000).

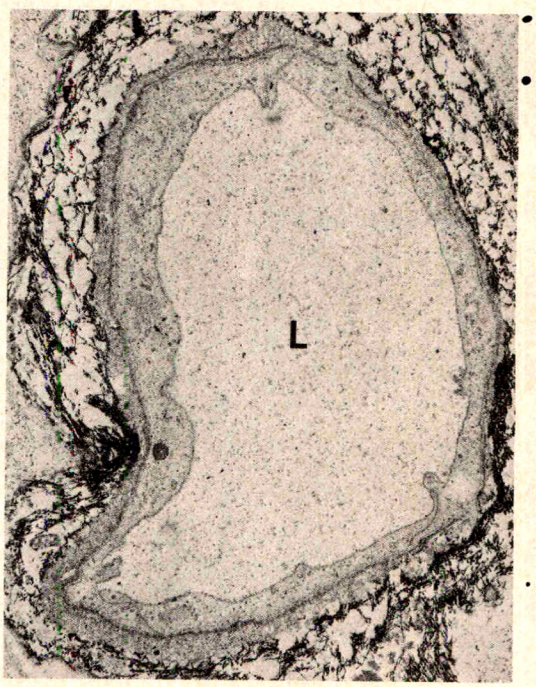


Fig. 20 (Ashton and Tripathi). A small retinal vessel in an aging human eye showing many fine fibrils. They are selectively argyrophilic and lie between the basal lamina of the vessel and that of the surrounding glia; L indicates lumen of the vessel (glutaraldehyde/osmium tetroxide fixed; stained silver methenamine after periodic acid treatment, ×10,600).

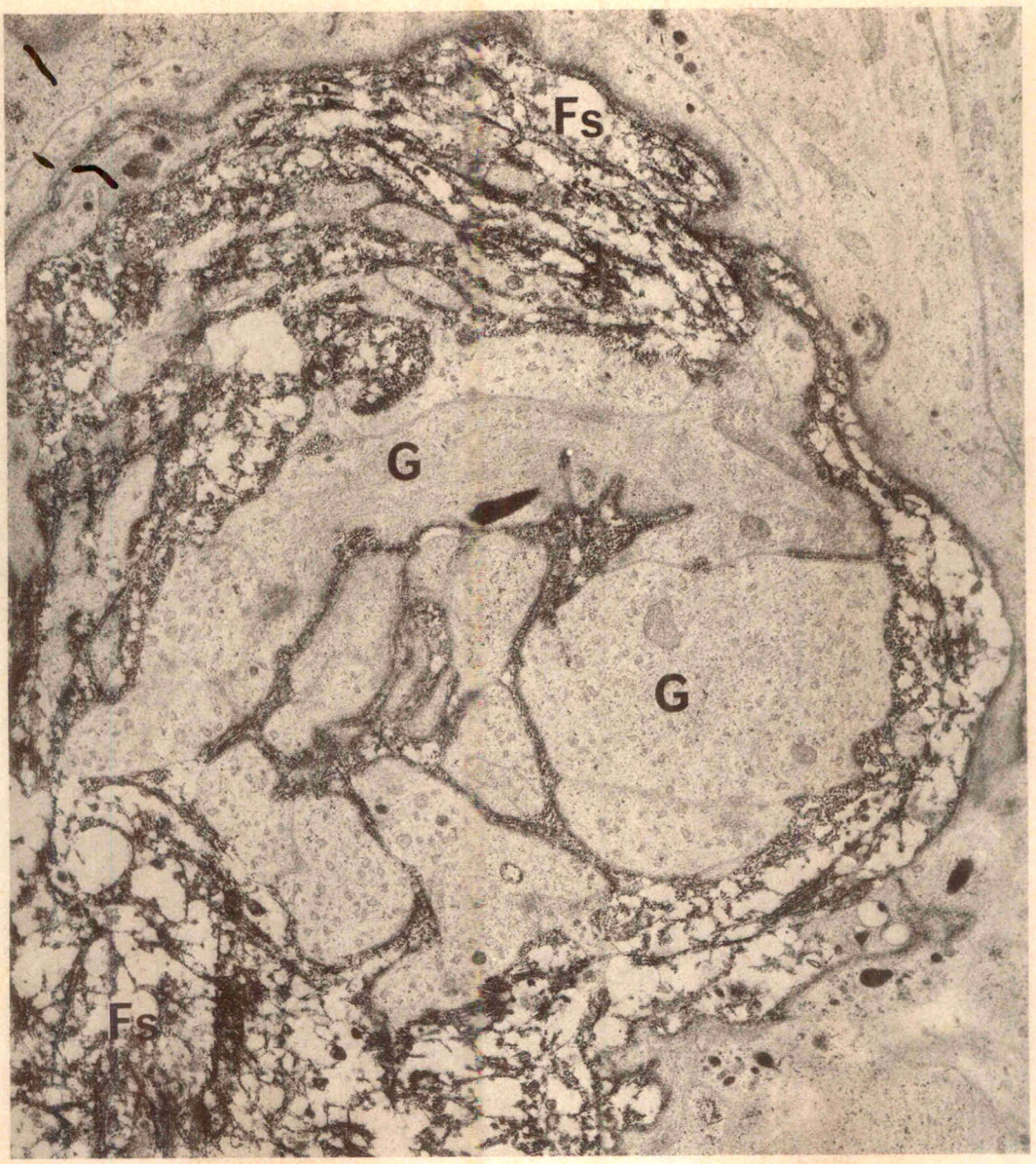


Fig. 21 (Ashton and Tripathi). A degenerate peripheral retinal vessel, invaded by glial cells (G). In the basal laminae note the presence of fine fibrils (Fs) showing selective affinity for silver methenamine. In contrast, the glial cells invading the vessel wall and lumen and those lying perivascularly are unstained with silver (osmium tetroxide fixed; stained with silver methenamine without prior treatment with periodic acid; senile human eye ×16,500).

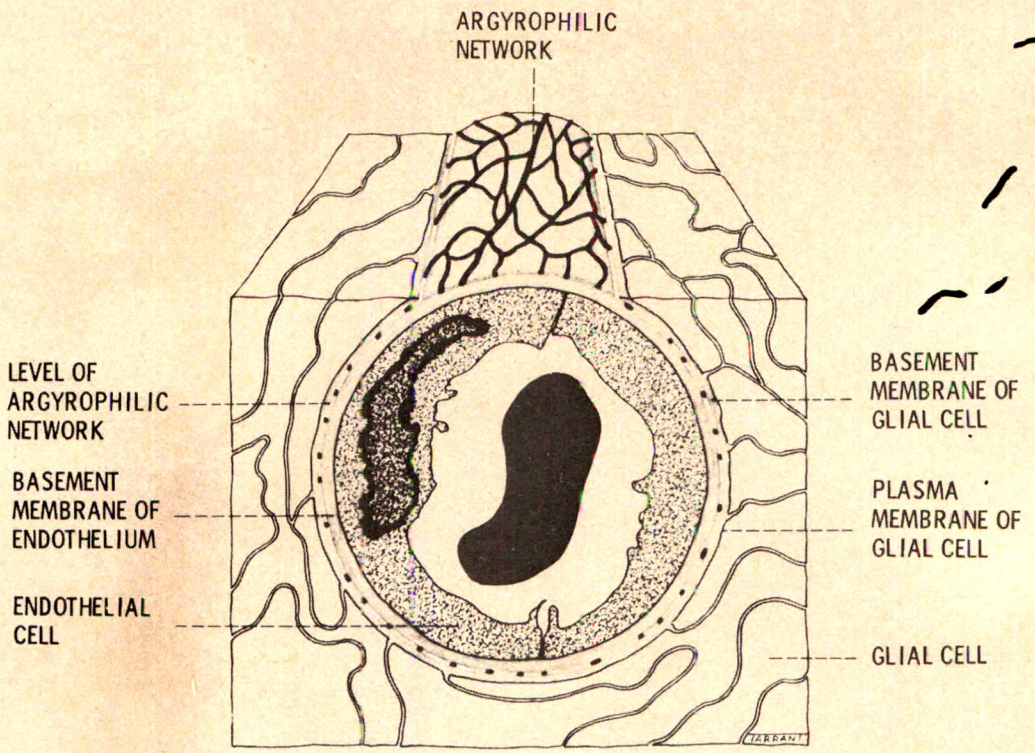


Fig. 22 (Ashton and Tripathi). Schema showing the location of the perivascular argyrophilic network between the vascular and glial basement membranes.

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ACETAZOLAMIDE, METABOLIC ACIDOSIS, AND INTRAOCULAR PRESSURE

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Since 1968 we have been studying the relationship between the acid-base status of the blood and aqueous humor and the lowering of the intraocular pressure (IOP) by blood-acidifying agents.[1–8] Benedikt, Zirm, and Harnoncourt[9] have also explored this question and recently reported a study of the relationship between the IOP and the metabolic acidosis induced by acetazolamide.

In glaucoma patients given acetazolamide intravenously, Benedikt, Zirm, and Harnoncourt[9] found that (1) the hypotensive effect of the drug did not last as long as the blood-acidifying effect; (2) by treating the induced metabolic acidosis with sodium bicarbonate infusion (140 mEq of sodium bicarbonate in 250 ml of physiological saline solution), the acidosis could be neutralized for from four to six hours; and (3) the maximum hypotensive effect was attained more rapidly if the acidosis was treated than if it was not. These authors concluded there was no constant correlation between the changes in the blood acid-base status and the IOP, and that the effect on the IOP induced by acetazolamide did not depend on the induced metabolic acidosis.

These conclusions were at variance with our own earlier finding that metabolic acidosis induced by various drugs was always accompanied by a reduction in the IOP, despite the variety of mechanisms by which the various drugs accomplished the acidification. We therefore decided to reexamine the mechanism by which acetazolamide reduces the IOP when administered intravenously to experimental animals, and to study the effect of treating the induced metabolic acidosis under different experimental conditions (that is, after the introduction of bases and the production of respiratory alkalosis).

Secondarily, we examined the effect of using sodium bicarbonate as a buffer, not only on the IOP of the glaucomatous patient but on the osmolarity of the patient's serum. In experimental animals we also investigated the behavior of the acid-base status of the aqueous humor after the use of three different blood-acidifying drugs: acetazolamide, calcium chloride, and ascorbic acid. Finally, in four groups of glaucomatous patients, we compared the ocular-hypotonizing and the blood-acidifying effects of acetazolamide, calcium chloride, ascorbic acid, and hydrochlorothiazide.

METHODS

Clinical study—THE REACTION OF THE IOP TO FOUR DRUGS WITH DIFFERENT BLOOD-ACIDIFYING MECHANISMS OF ACTION—The subjects were 32 patients with open-angle (chronic simple) glaucoma. All antiglaucomatous therapy, both local and systemic, was discontinued 72 hours before the administration of the hypoton-

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izing drugs. The capillary blood to be used for the acid-base determinations was collected from the fingertip.

While fasting, the 32 patients were treated as follows: Eight received 500 mg of acetazolamide (Diamox); eight received 70 mg/kg of body weight of a 10% calcium chloride solution; eight received 400 mg/kg of body weight of a 20% ascorbic acid solution; and eight received 50 mg of hydrochlorothiazide (Esidrex). The dosages were based on the ocular hypotonizing effect of each drug. As for hydrochlorothiazide, the mean diuretic dose was chosen.

Before treatment and at regular intervals thereafter, the following determinations were made: (1) IOP (measured by Goldmann's applanation tonometer); (2) blood pH (pH of the capillary blood at 38°C); (3) standard bicarbonate concentration; that is, the concentration of bicarbonate in the blood plasma after the cells had been separated and the hemoglobin completely oxygenated at a CO_2 pressure of 40 mm Hg and a temperature of 38°C; (4) base excess; that is, the amount of fixed acid or base excess in milliequivalent per liter, with a negative value indicating an acid excess.

The pH and the alkali reserve (standard bicarbonate concentration and base excess) were determined by means of the Micro-Astrup pH apparatus, which consists of a microtonometer, a thermostated capillary glass electrode and thermostated calomel electrode, a circulation thermostat, and a pH meter. Blood collected in a heparinized glass capillary tube was sucked anaerobically into the capillary glass electrode. To determine the alkali reserve, two samples of the same blood were brought into contact with two gas mixtures of known PCO_2 (4 and 8%) in a shaking chamber and were shaken for three minutes. The samples were then sucked up into the electrode and the pH was measured. We determined the relevant acid-base values by means of the curve nomogram of Siggaard-Andersen and Engle, using the pH values after CO_2-equilibration.

IOP AND SERUM OSMOLARITY AFTER SODIUM BICARBONATE INFUSION OF GLAUCOMA PATIENTS—A control group of five patients with open-angle glaucoma received a continuous infusion of 140 mEq of sodium bicarbonate in 250 ml of physiological saline solution.[9] The osmotic pressure of the solution and the serum levels were evaluated at regular intervals with the Fiske Osmometer. The IOP was measured at regular intervals with the MacKay-Marg electronic tonometer.

Experimental study—The experimental animals were 48 pigmented rabbits weighing 2.5 to 3.0 kg each. After inducing local anesthesia with 3% carbocaine, we took blood for the various determinations from the femoral artery by means of a polyvinyl cannula; and after anesthetizing the eye with 0.4% Novesine Wander, we collected the aqueous humor by means of a 22-gauge needle.

As in the clinical study, the pH and alkali reserve (standard bicarbonate concentration and base excess) of both blood and aqueous humor were determined by means of the pH apparatus already described; the osmotic pressure was measured with the Fiske Osmometer; and the IOP was measured with the MacKay-Marg electronic tonometer.

EXPERIMENT A. TO DETERMINE THE LOWEST EFFECTIVE INTRAVENOUS DOSE OF ACETAZOLAMIDE, BOTH OCULAR HYPOTONIZING AND BLOOD-ACIDIFYING—Rabbits were given acetazolamide (Diuriwas) intravenously in doses of 1.0, 2.5, and 5.0 mg/kg of body weight. The effects of the various dosages on the rabbits' IOP, blood pH, and blood alkali reserve were monitored as described above.

EXPERIMENT B. TO TREAT THE ACETAZOLAMIDE-INDUCED METABOLIC ACIDOSIS—We gave five animals continu-

ous intravenous infusions (25 drops/min) of an iso-osmotic (1.4%) solution of sodium bicarbonate (320 mOsm/liter), and five other animals similar infusions of an iso-osmotic (1.45%) solution of sodium carbonate (311 mOsm/liter). The infusions were begun one hour before the intravenous administration of the lowest effective dose of acetazolamide (as established in experiment A: 2.5 mg/kg of body weight) and were maintained for three hours thereafter.

Respiratory alkalosis was produced in a group of rabbits that had been anesthetized with subcutaneous doses of ethylurethane (6 mg/kg of body weight of a 25% solution) and curarized with gallamine trijodide (4 mg/kg of body weight intravenously and 40 mg/kg of body weight intramuscularly). We then performed a tracheotomy on each animal, cannulated the trachea, and applied artificial pulmonary ventilation.

EXPERIMENT C. TO DETERMINE THE ACID-BASE STATUS OF THE BLOOD AND AQUEOUS HUMOR AFTER THE ADMINISTRATION OF THREE BLOOD-ACIDIFYING DRUGS—One group of rabbits received acetazolamide in oral doses of 100 mg/kg of body weight; a second group received calcium chloride (10% solution) in oral doses of 500 mg/kg of body weight; and a third group received ascorbic acid (20% solution) in oral doses of 1 g/kg of body weight. The oral doses were given through gastric tubes.

RESULTS

Experimental study—EXPERIMENT A. LOWEST EFFECTIVE DOSE OF ACETAZOLAMIDE—The intravenous administration of 1 mg/kg of body weight of acetazolamide induced no changes in either the IOP or the blood acid-base status of the rabbit.

The intravenous administration of 2.5 mg/kg of body weight was followed by a reduction in the IOP, which was constantly accompanied by a reduction in the blood pH and in the blood alkali reserve (standard bicarbonate and base excess). At the moment of the maximum effect, the mean reduction in the IOP was 30%, the reduction in the standard bicarbonate concentration was 23%, and the reduction in the base excess was 159%. After the second hour, the pretreatment levels of both the IOP and the acid-base status were gradually reestablished (Fig. 1).

The intravenous administration of 5.0 mg/kg of body weight also enhanced both the ocular-hypotonizing and the blood-acidifying effects.

EXPERIMENT B. BUFFERING OF THE METABOLIC ACIDOSIS—The results of the infusions with sodium bicarbonate and sodium carbonate were identical. One hour after each set of infusions was begun, that is, just before the acetazolamide was administered, the acid-base status of the blood shifted toward significant alkaline values. The following mean increases were observed: 0.27 in the pH, 24 mEq/liter in the standard bicarbonate concentration, and 14 mEq/liter in the base excess.

However, 30 minutes after the administration of 2.5 mg/kg of body weight of acetazolamide, while the buffering solutions were still being continuously infused, a gradual reduction in the alkali reserve values, away from the high levels previously observed, took place. Three hours after the administration of acetazolamide, these levels were still lower—lower even than the pretreatment levels. With respect to these initial levels, there was a mean decrease of 3 and 2 mEq/liter, in the standard bicarbonate concentration and the base excess, respectively.

A respiratory alkalosis was also induced experimentally in tracheotomized and curarized animals by means of controlled pulmonary hyperventilation. This occurred one hour before and three hours after the intravenous administration of 2.5 and 5.0 mg/kg of body weight of

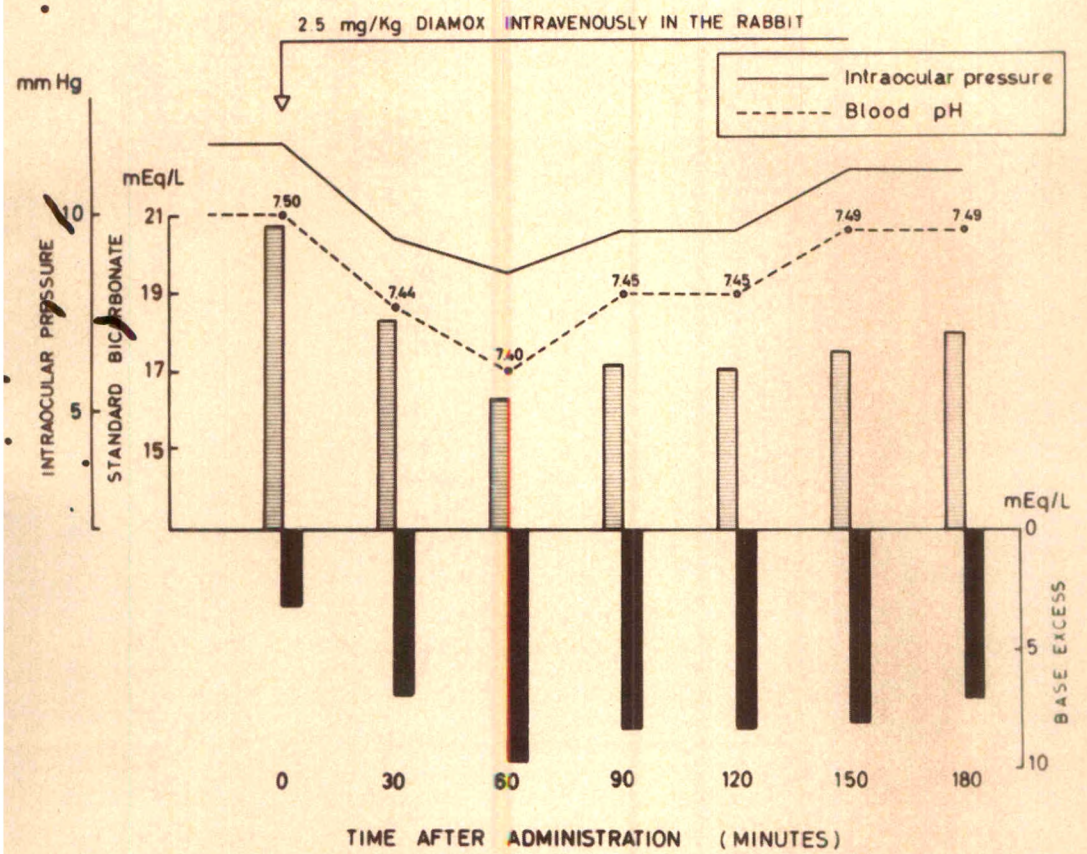


Fig. 1 (Bietti and associates). Correlation between the long-term effects of the lowest intravenous effective dose of acetazolamide (2.5 mg/kg of body weight) on the IOP and blood-acid base status of the rabbit (mean of six animals).

acetazolamide. Despite sustained pulmonary hyperventilation, however, a marked metabolic acidosis began 30 minutes after administration of the drug. (The IOP values could not be determined because of interference from the arterial pressure changes caused by the hyperventilation.)

EXPERIMENT C. THE ACID-BASE STATUS OF THE BLOOD AND AQUEOUS HUMOR AFTER THE USE OF VARIOUS BLOOD-ACIDIFYING DRUGS—**Acetazolamide**—Three hours after the oral administration of acetazolamide (100 mg/kg of body weight) to six rabbits, there was a mean reduction in the blood pH of 0.09 pH units, and 12 and 9 mEq/liter in the standard bicarbonate concentration and base excess, respectively. The aqueous humor behaved similarly; at the third hour, there was a mean reduction in the pH of 0.13 pH units, and a mean reduction of 10 and 11 mEq/liter in the standard bicarbonate concentration and base excess, respectively (Fig. 2). The osmotic pressure of both serum and aqueous humor remained unchanged.

Calcium chloride—Three hours after the oral administration of 10% calcium chloride solution (500 mg/kg of body weight) to six rabbits, there was a mean decrease in blood pH of 0.12 pH units, and a reduction of 9 and 13 mEq/liter in standard bicarbonate concentration and base excess, respectively. The aqueous behaved similarly; at the third hour there was a mean reduction in the pH of 0.13.

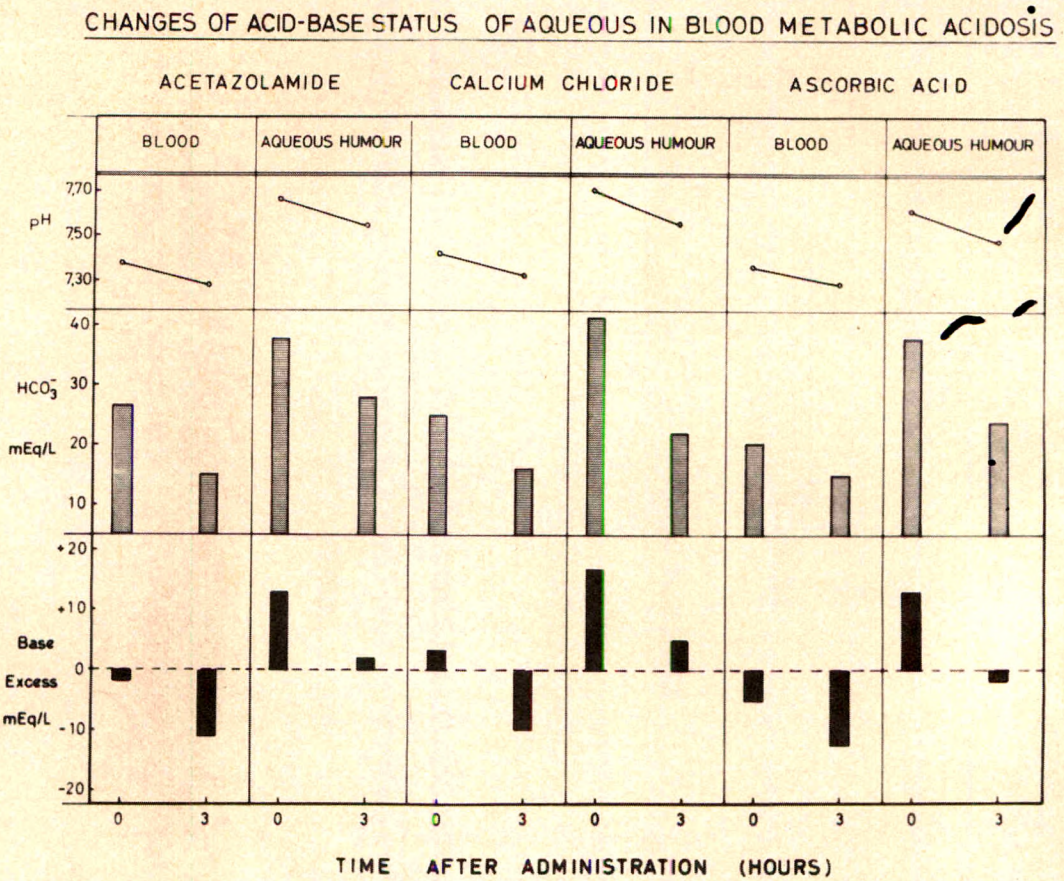


Fig. 2 (Bietti and associates). Correlation between the effects of administering various blood-acidifying drugs with different mechanisms of action on the acid-base status of the blood and the acid-base status of the aqueous humor of the rabbit. Drugs administered: acetazolamide, 100 mg/kg of body weight, orally; calcium chloride, 500 mg/kg of body weight, orally; ascorbic acid, 1 g/kg of body weight, orally (mean of six animals for each drug).

pH units, and a reduction of 19.5 and 12 mEq/liter in the standard bicarbonate concentration and base excess, respectively. The osmotic pressure of both serum and aqueous humor remained unchanged (Fig. 2).

Ascorbic acid—Three hours after the oral administration of a 20% ascorbic acid solution (1 g/kg of body weight) to six rabbits, there was a mean decrease in the blood pH of 0.06 pH units, and 5.0 and 7.5 mEq/liter in the standard bicarbonate concentration and base excess, respectively. The aqueous humor behaved similarly; at the third hour, there was a mean reduction in the pH of 0.14 pH units, and 12 and 15 mEq/liter in the standard bicarbonate concentration and base excess, respectively (Fig. 2). The osmotic pressure of both serum and aqueous humor remained unchanged.

Clinical study—THE REACTION OF THE IOP TO FOUR DRUGS WITH DIFFERENT BLOOD-ACIDIFYING MECHANISMS OF ACTION—**Calcium chloride** in a dose of 70 mg/kg of body weight orally had induced a maximum reduction in the IOP (an average of 7.3 mm Hg) by the fourth posttreatment hour. At the same time there was a maximum reduction in the

blood alkali reserve (a mean of 3.9 mEq/liter for the standard bicarbonate concentration and of 4.5 mEq/liter for the base excess).

Acetazolamide in a single dose of 500 mg orally had induced a maximum reduction in the IOP (an average of 9 mm Hg) by the fourth posttreatment hour. At the same time there was a maximum reduction in the blood alkali reserve (a mean of 3.5 mEq/liter for the standard bicarbonate concentration and of 4.5 mEq/liter for the base excess).

Ascorbic acid in a dose of 400 mg/kg of body weight orally had induced a maximum reduction in the IOP (an average of 6.7 mm Hg) by the fourth hour. At the same time there was a maximum reduction in the blood alkali reserve (a mean of 4.8 mEq/liter for the standard bicarbonate concentration and of 6.5 mEq/liter for the base excess).

Hydrochlorothiazide in a dose of 50 mg orally had induced a reduction in the IOP (an average of 1 mm Hg) by the fourth hour. At the same time there was a maximum reduction in the blood alkali reserve (a mean of 1 mEq/liter for the standard bicarbonate concentration and of 0.5 mEq/liter for the base excess) (Fig. 3).

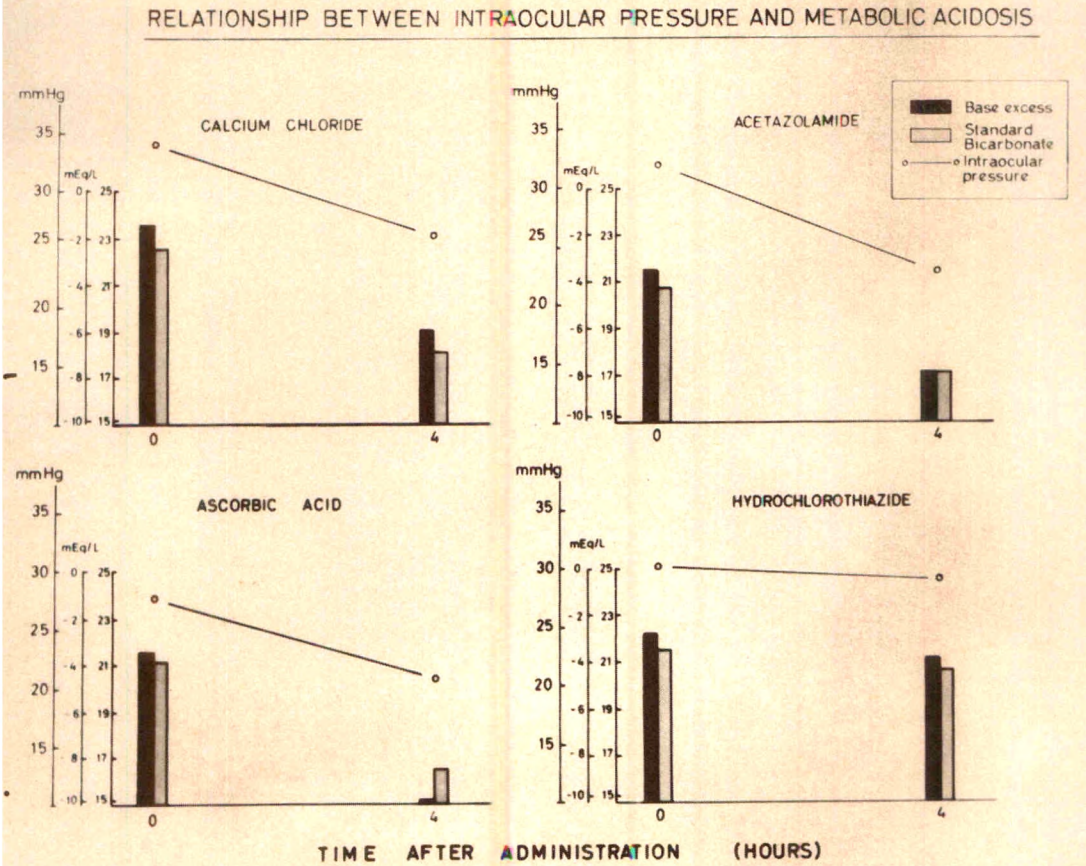


Fig. 3 (Bietti and associates). Effects of drugs with different mechanisms of blood-acidifying action on the IOP and blood alkali reserve (standard bicarbonate concentration and base excess) of patients with open-angle chronic simple glaucoma. Drugs administered: calcium chloride, 70 mg/kg of body weight, orally; acetazolamide, 500 mg/kg body weight, orally; ascorbic acid, 400 mg/kg of body weight, orally; hydrochlorothiazide, 50 mg/kg of body weight, orally (mean of eight patients for each drug).

IOP AND SERUM OSMOLARITY AFTER SODIUM BICARBONATE INFUSION OF GLAUCOMA PATIENTS—The concentration of the sodium bicarbonate solution used as a buffer by Benedikt, Zirm, and Harnoncourt[9] was 140 mEq of sodium bicarbonate in 250 ml of physiological saline solution. The osmotic pressure of this solution was shown to be 1,230 mOsm/liter. For a patient weighing approximately 70 kg, this corresponds to 2 mEq/kg of body weight (or, expressed in grams, to 168 mg/kg of body weight), administered over a period of six hours.

The infusion of such a sodium bicarbonate solution in glaucomatous patients resulted in a mean reduction in the IOP of 9 mm Hg, and a mean increase in the patient's serum osmolarity of 16 mOsm/liter by the fourth hour (Fig. 4).

Discussion

In our clinical trials on glaucomatous eyes, the blood-acidifying effect of the drugs tested was always accompanied by an ocular-hypotonizing effect. In order to investigate the long-term behavior of the two factors, we chose experimental animals (rabbits) with normal eyes and established for these animals the lowest blood-acidifying effective dose of acetazolamide. In the rabbits, this dose (2.5 mg/kg of body weight) was always accompanied by an ocular hypotonizing effect, and the duration and intensity of the two effects coincided (Fig. 1). The use of the lowest effective dose permitted us to follow the experiment over a period of time so that we were able to observe the reestablishment of the pretreatment conditions. (Strictly reproducible responses

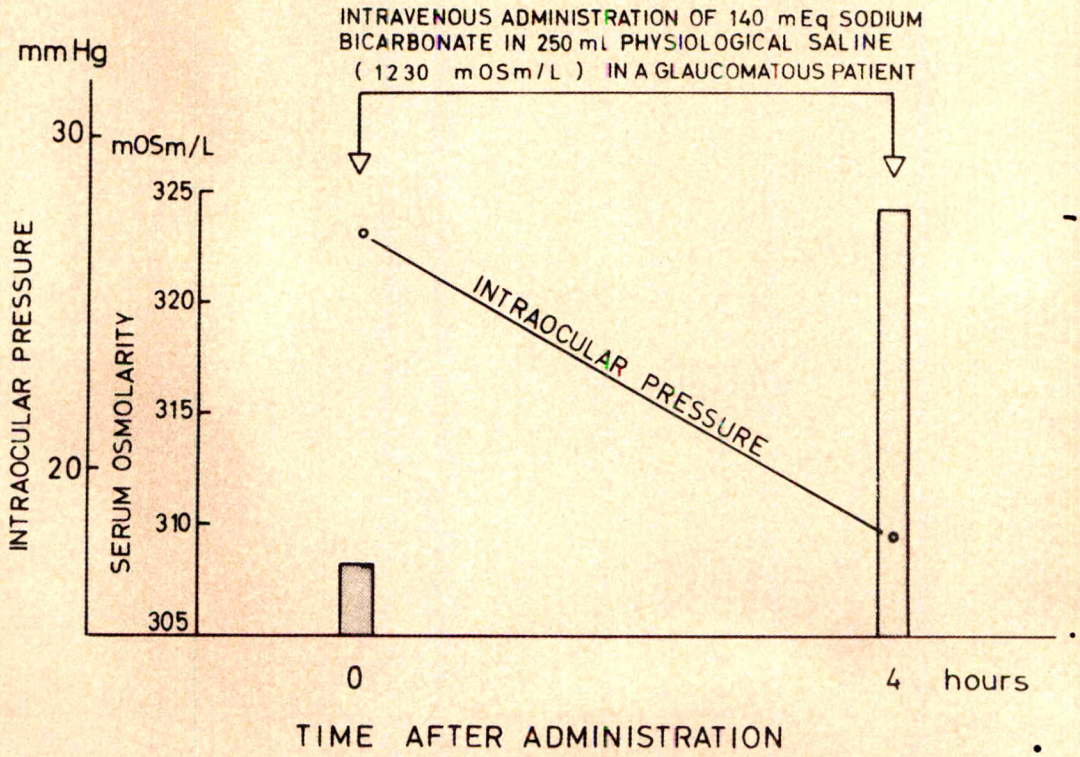


Fig. 4 (Bietti and associates). Comparison of the IOP and serum osmolarity of a patient with open-angle chronic simple glaucoma before and four hours after the continuous intravenous infusion of 140 mEq of sodium bicarbonate in 250 ml of physiological saline solution.

probably cannot be obtained in glaucomatous eyes because of their compromised hydrodynamics.)

In our investigations of acetazolamide's mechanism of action in rabbits, we treated the metabolic acidosis induced by the acetazolamide to establish the role of this induced acidosis in the lowering of IOP. When we introduced bases into the rabbit's blood stream, we found that intravenous administration of an iso-osmotic sodium bicarbonate or sodium carbonate solution (one that would not disturb the blood osmolarity), even if infused in large amounts (100 ml/kg of body weight), could not prevent the shift of the blood acid-base status toward the acid side after the intravenous administration of the lowest effective dose (both ocular hypotonizing and blood acidifying) of acetazolamide.

The enormous amount of fluid that had to be given to the animal to maintain the constancy of the acid-base status excluded all possibility of using this method clinically to treat the acidosis induced by acetazolamide in glaucomatous patients.

A personal exchange of views with Benedikt and Zirm acquainted us with their methods and the concentration of the sodium bicarbonate solution they used. Since the osmotic pressure of their solution was shown to be 1,230 mOsm/liter, and since that is about four times higher than the serum osmolarity in man (300 to 320 mOsm/liter), we decided to study the changes in the serum osmolarity and simultaneously to measure the IOP levels during the continuous infusion of such a hypertonic sodium bicarbonate solution in glaucomatous patients. During the infusion the increase in serum osmolarity promoted a reduction in the IOP (Fig. 4).

According to Benedikt, Zirm, and Harnoncourt[9] the reduction in the IOP after the use of acetazolamide is not related to the blood-acidifying effect of the drug since the IOP also dropped when the effect was treated with the described sodium bicarbonate solution. In our opinion, the attempt of these authors to treat the metabolic acidosis in order to exclude its possible causal relationship to the ocular hypotension is not valid since their sodium bicarbonate solution was able to reduce the IOP by itself through an osmotic mechanism.

Our attempts to antagonize the metabolic acidosis induced by acetazolamide were unsuccessful. The infusion of large amounts (100 ml/kg of body weight) of iso-osmotic bases (sodium bicarbonate and sodium carbonate) failed to neutralize the blood acidification induced by the lowest effective dose of acetazolamide (2.5 mg/kg of body weight). Nor were we able to antagonize the metabolic acidosis by pulmonary hyperventilation (respiratory alkalosis) carried out in the curarized animal.

Is the acidosis then responsible for the intraocular hypotony? Before giving our answer to this question, let us examine the results of our other experiments in which we induced a metabolic acidosis with several drugs that acidify the blood in other ways.

Calcium chloride is described pharmacologically as an acidifying diuretic. Ascorbic acid, a weak acid, if administered orally in high dosages in man (400 mg/kg of body weight) exerts a blood-acidifying effect without disturbing the hematic osmolarity.[2] When we gave calcium chloride and ascorbic acid to patients with open-angle glaucoma, there was always a positive correlation between the resultant ocular hypotony and the induced metabolic acidosis.

The behavior of hydrochlorothiazide is particularly interesting. This drug is a thiazidic diuretic that has only a slight ocular hypotonizing effect in spite of its marked diuretic activity. On the other hand, it is well known that what ocular

tension-lowering action it exerts is not attributable to the degree of the diuresis induced.

In such pathological situations as pronounced diabetic acidosis, moreover, one of the most prominent ocular signs is marked hypotony.[10]

The experiments reported here, together with these other relevant considerations, favor the existence of a causal relationship between blood acidosis and ocular hypotony. Supportive of this conclusion were our animal experiments in which there was always a marked reduction in the pH and alkali reserve of the aqueous humor after the administration of acetazolamide or other blood-acidifying drug. This means that there is a close relationship between the acid-base status of the blood and the acid-base status of the aqueous humor.

Moreover, the fact that subconjunctival injections of acetazolamide do not induce IOP changes in either animals or man,[11,12] even if the resultant carbonic anhydrase is almost completely inhibited at the ocular level, is further evidence that the ocular hydrodynamics are influenced by the systemic disturbances.

All of the body's organic fluids, in order to keep constant the acid-base status of the blood, bring about a shifting of the bases and acids, and consequently of the fluids, by means of a variety of intra- and extracellular buffer systems as well as through the phenomena of homeostatic regulation.

In our opinion, the ocular hypotony induced by acetazolamide, as well as by other blood-acidifying drugs, is attributable to the hydrodynamic changes that take place in the aqueous humor as a consequence of the induced metabolic acidosis.

SUMMARY

In order to investigate whether or not there is a causal relationship between the metabolic acidosis and the ocular hypotension induced by acetazolamide, we undertook to correlate over a period of time the blood-acidifying and ocular-hypotonizing effects of administering the lowest intravenous effective dose of acetazolamide; to treat the metabolic acidosis induced by acetazolamide by means of the intravenous introduction of bases, and pulmonary hyperventilation (respiratory alkalosis); to evaluate the effects on the intraocular pressure (IOP) by neutralizing the acetazolamide-induced metabolic acidosis by means of a continuous infusion of sodium bicarbonate; to determine the relationship between the metabolic acidosis induced by blood-acidifying agents, which do not inhibit carbonic anhydrase, and the IOP; and to determine the changes in the acid-base status of the aqueous humor induced by acetazolamide and other blood-acidifying drugs.

We found that the hypertonic buffering solution of sodium bicarbonate could reduce the IOP by itself through an osmotic mechanism. On the basis of our results, we believe that a causal relationship exists between the metabolic acidosis induced by acetazolamide, and by other drugs that have a blood-acidifying effect as the result of other mechanisms, and ocular hypotension, both in the animal and in the glaucomatous patient.

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HEREDITARY CATARACTS IN DEER MICE (*PEROMYSCUS MANICULATUS*)

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It is a pleasure to dedicate this work to Michael Hogan. Teacher, friend, and investigator, he has been a leader in the integration of structure and function in the eye.

This is the first report of predictable hereditary cataracts in the *Peromyscus maniculatus* (peros-maimed; mus-mouse) or deer mouse, a rodent found throughout the United States.* The cataract resembles lens opacities that occur after acute metabolic insults or those that develop slowly during the aging process. We feel that this progressive lens opacification may be a model for the study of senile cataract.

We studied a colony of deer mice for one year. Their cataracts are inherited as an autosomal-recessive trait. At first, cataracts were visible at 3 years of age. (The maximum life span of deer mice is 8 years). By selective breeding, the frequency of cataracts increased, and became visible at 2 months to 1 year of age. Brother and sister breeding attempts were carried out, but inbreeding decreased the frequency of mating in litters, so periodic outbreeding into unaffected deer mice is necessary.[3] This decreases the frequency of the autosomal-recessive trait.

Cataractous development can be predicted in deer mice born with clear lenses, because syndactyly of the middle toes of the hind feet occurs in animals destined to develop cataracts, and can be identified at 13 to 14 days of age. Sometimes the third and fourth toes on the front feet are fused, but this is less predictable for cataracts than syndactyly of the hind feet. The coincidence of the two defects is probably due to either gene linkage or pleiotropic effects of a single gene. Animals without toe fusion do not appear to inherit cataracts and are considered normal in this study.

MATERIALS AND METHODS

Animals were maintained in animal quarters for one year. Deer mice breed by 6 weeks of age, and usually have two to four in a litter. The female deer mouse can breed the first day after giving birth to a litter. Sibling mating was encouraged, as was back breeding to the parent.

We examined the animals with a Haag-Streit 900 slit lamp. The deer mouse lens was large and the eyes dilated well with cycloplegics. Animals were anesthetized with methoxyflurane for slit-lamp photography. Selected animals were killed with an overdose of anesthetic. Whole heads of animals younger than 10 days old were fixed in 10% neutral formalin. After the eyelids opened at about 14 days, eyes were enucleated and placed in either 10% formalin for paraffin embedding or a 2% paraformaldehyde-1% glutaraldehyde mixture for plastic embedding. Some lenses were dissected from the globe before fixation, and others were dissected after fixation and before embedding. Par-

*These *Peromyscus* were first studied by R. R. Huestis, Ph.D., University of Oregon, Eugene, Oregon. While examining the inheritance of iris color, he noted that some of the animals had cataracts.[1] A further hereditary defect includes neonatal jaundice that resembles hereditary spherocytosis in man.[2] We obtained a colony through Ruth Anderson, Ph.D., Division of Immunology, University of Oregon Health Sciences Center, Portland, Oregon.

From the John E. Weeks Memorial Laboratory of Ophthalmology, University of Oregon Medical School, Portland, Oregon. This study was supported in part by grants EY00753 and EY00715, and Research to Prevent Blindness, Inc.

Reprint requests to Robert P. Burns, M.D., John E. Weeks Memorial Laboratory of Ophthalmology, University of Oregon Medical School, Portland OR 97201.

affin sections were stained with hematoxylin and eosin. Epoxy sections were stained with toluidine blue-borax stain.

RESULTS

Biomicroscopy—The head and fused toes of a deer mouse with white lenses are shown in Figures 1 and 2. The biomicroscopic findings varied from clear lens with normal Y sutures, to a diffuse nonlocalized haziness in the lens, to anterior subcapsular and posterior subcapsular opacities (Fig. 3, left and center), to a complete mature white cataract (Fig. 3, right). Wrinkled hypermature cataracts with iritis and atrophy of the entire globe occurred in the final stages of opacification. Iris anomalies also occurred. We noted colobomas of the iris in some animals with cataracts. Irides occasionally appeared atrophic with a hypermature cataract.

Histology—Biomicroscopically, clear lenses from presumably normal deer mice with normal toes were histologically similar to house mice[4] (Figs. 4 and 5). The lens in a 6- to 10-day-old deer mouse was round and filled the ocular cavity. The ciliary body and iris were rudimentary and a tunica vasculosa lentis was present. The lens bow contained many nuclei that spread deep and toward the anterior pole.



Fig. 1 (Burns and Feeney). Adult deer mouse has bilateral cataracts.

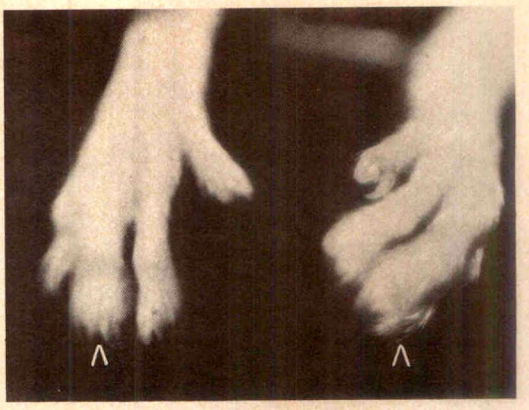


Fig. 2 (Burns and Feeney). Fused third and fourth toes (arrows) of the hind feet of a deer mouse.

The lens capsule was thin and zonular fibers were not visible. In plastic-embedded sections, light and dark cells were scattered throughout the bow region (Fig. 6). We do not know whether these are indications of early disease or if more subtle abnormalities are present.

At 25 days of age, about ten days after the eyelids opened, the lens appeared similar to a normal adult lens. There were fewer nuclei in the bow and the tunica vasculosa lentis disappeared. The lens was more lenticular but still occupied most of the eye. There was little difference in the 25-day-old specimen and a 2.5-year-old specimen from a deer mouse that had no fused toes and was not expected to develop a cataract.

Pathology—The earliest pathologic changes in deer mice with fused toes that should have developed cataracts were vacuolation in and near the nuclei just inside the lens bow at the equator (Figs. 7 and 8). These cells at the equator of the lens, that are differentiating from anterior epithelium into lens fibers, seem to be the morphologic site of the initial pathology (Fig. 9).

The equatorial cells of the lens migrated posteriorly under the lens capsule in the animals that developed posterior subcapsular cataracts (Fig. 10). The basal

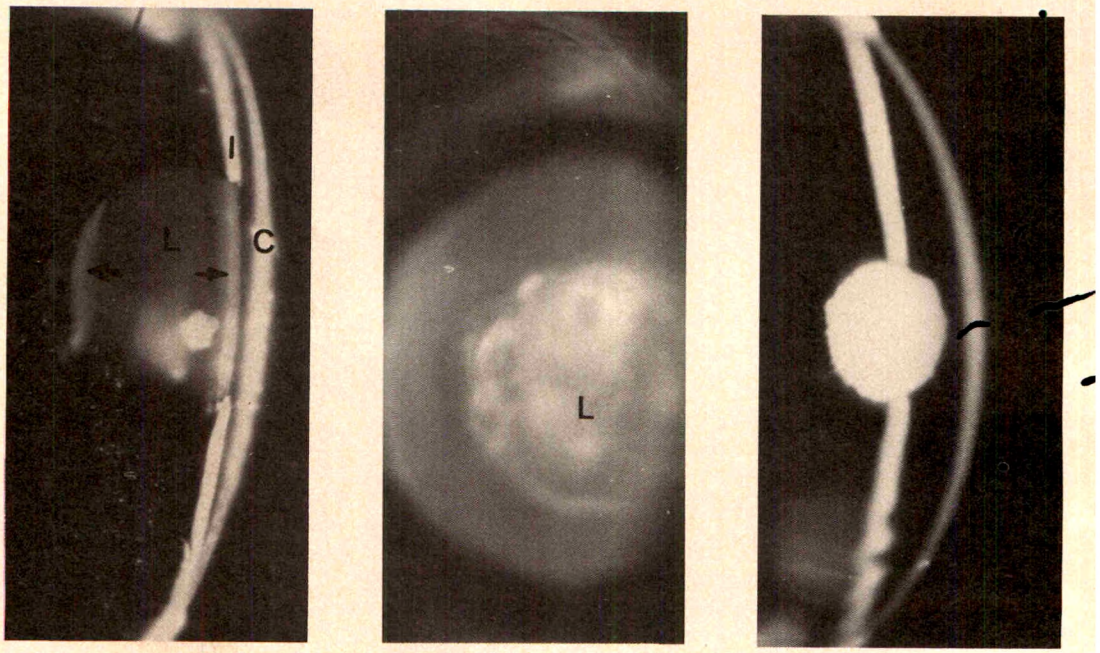


Fig. 3 (Burns and Feeney). Left, Slit-lamp photograph of a young adult deer mouse showing a posterior subcapsular cataract. Slit beam passes through cornea (C), iris (I), anterior lens surface (L), and cataract on posterior lens. Center, Front view, slit-lamp photograph of central posterior subcapsular cataract with an uneven, whorled appearance. Pupil is widely dilated; L indicates lens. Right, Slit-lamp photograph of a mature cataract.

ends of the superficial cortical cells (that is, the posterior subcapsular lens fibers) had striations and disruptions in paraffin-embedded sections (Fig. 11, left). The same specimen, embedded in plastic, had a different morphology: the most su-

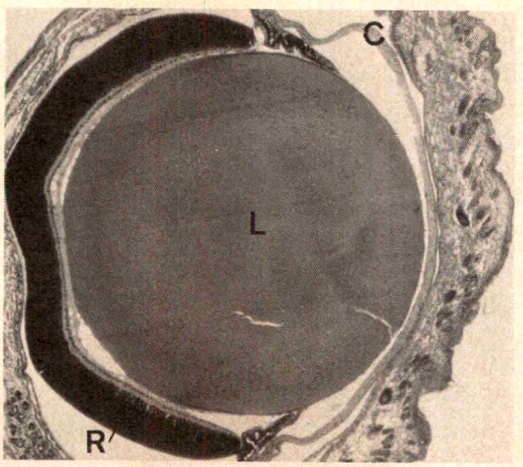


Fig. 4 (Burns and Feeney.) Coronal section through the head of a 6-day-old deer mouse showing normal histology. Eyelids are still fused; cornea (C), lens (L), and retina (R) (paraffin, hematoxylin and eosin, ×32).

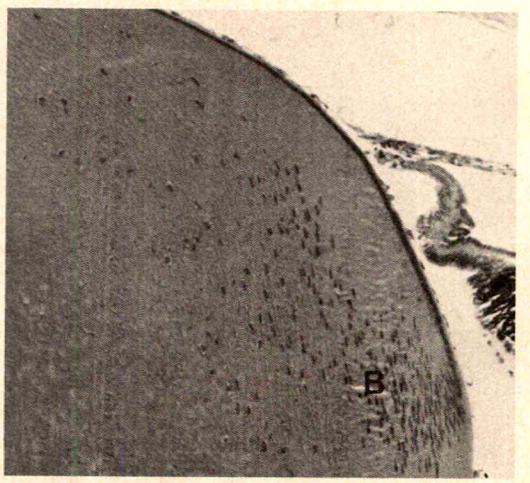
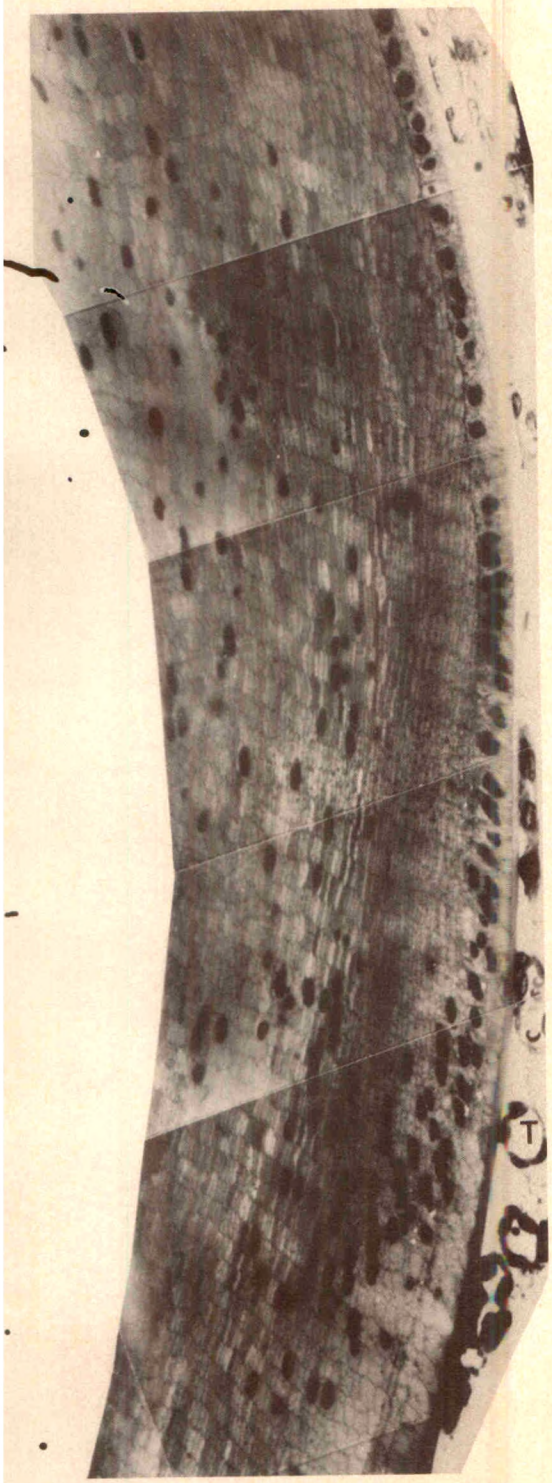


Fig. 5 (Burns and Feeney). Section through lens equator in a 6-day-old normal lens showing distribution of nuclei at the bow (B) (paraffin, hematoxylin and eosin, ×150).



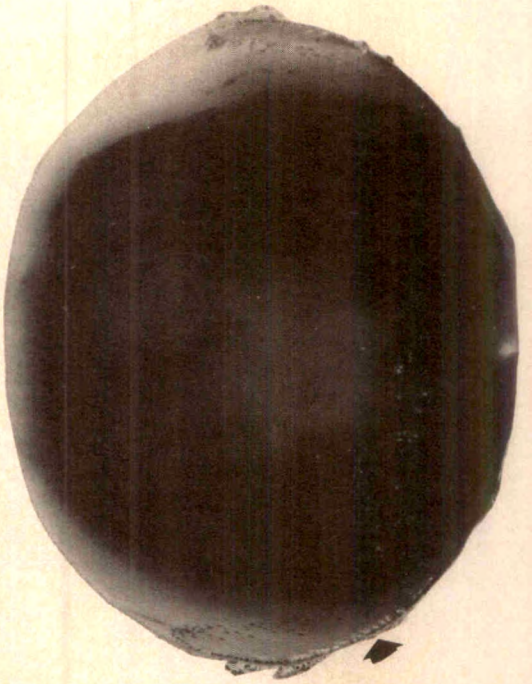


Fig. 7 (Burns and Feeney). Clear lens by slit lamp in infant deer mouse with fused toes. Note vacuolization of superficial fibers just anterior to the bow (arrow) (plastic, toluidine blue, ×77).

perficial cells were swollen and irregular, whereas underlying cells appeared dense and shrunken (Fig. 11, right).

Large epithelioid round cells collected in the posterior subcapsular region in plaques, similar to cells described as "bladder" or "Wedl" cells[5] in human cataracts (Fig. 12). The anterior and posterior poles of the same lens showed a large posterior subcapsular cataract but a relatively normal anterior surface (Fig. 13). However, the nuclei of the epithelial cells in the anterior lens appeared somewhat pyknotic.

The anterior cortex in some lenses showed degeneration of superficial lens

Fig. 6 (Burns and Feeney). Montage of lens equator in a normal infant deer mouse. Note normal appearance of epithelium and superficial lens fibers; T indicates tunica vasculosa lentis (plastic, toluidine blue, ×420).

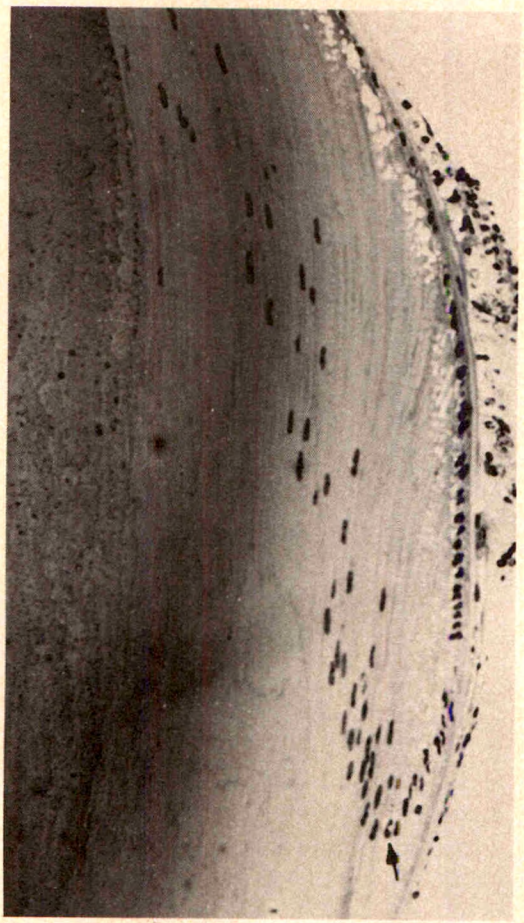


Fig. 8 (Burns and Feeney). Enlargement of a portion of Figure 7. Note vacuolization near nuclei at the lens bow (plastic, toluidine blue, ×100).

fibers with pooling of the cytoplasmic protein into globules, while the overlying epithelium appeared relatively unaffected (Fig. 14). Proliferation of anterior epithelium did not occur. As anterior cortical

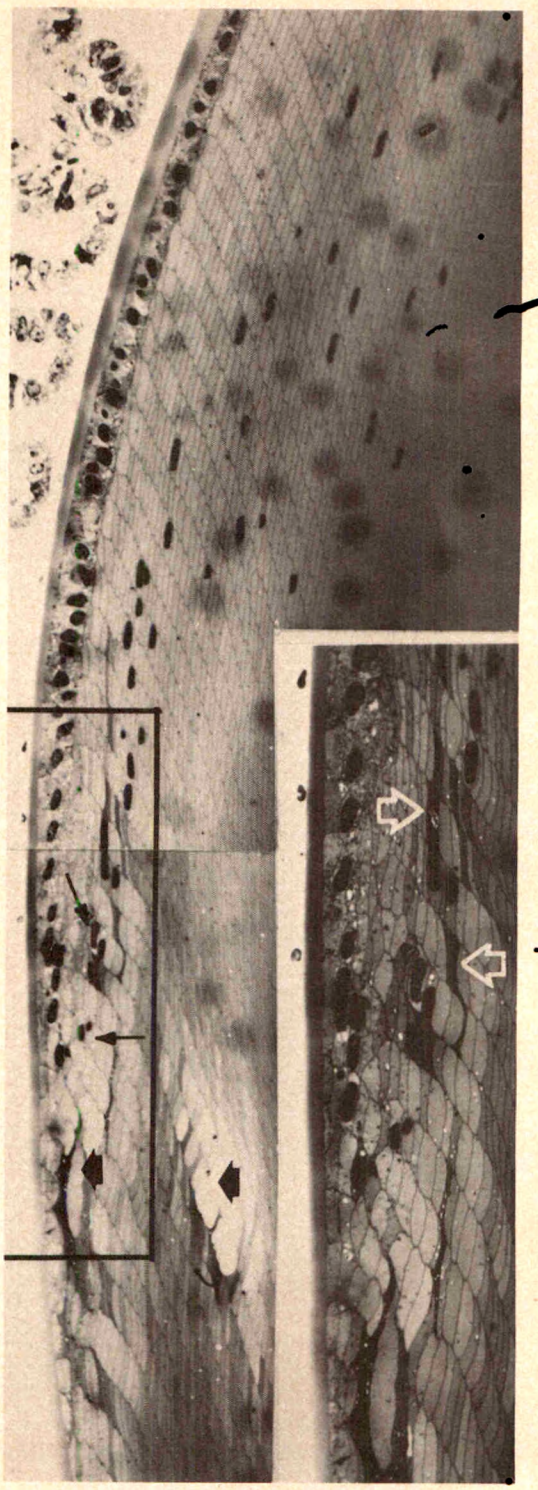


Fig. 9 (Burns and Feeney). Montage of equatorial region of adult hazy lens. Compare the abnormalities in spacing of nuclei (thin arrows) and in density of newly formed lens fibers (thick arrows) with those of normal lens in Figure 6. (Dots are an artifact of uneven staining.) Enclosed area is enlarged in inset (×250). Inset, Note dense cytoplasm of several abnormal lens fibers (arrows) (plastic, toluidine blue, ×420).

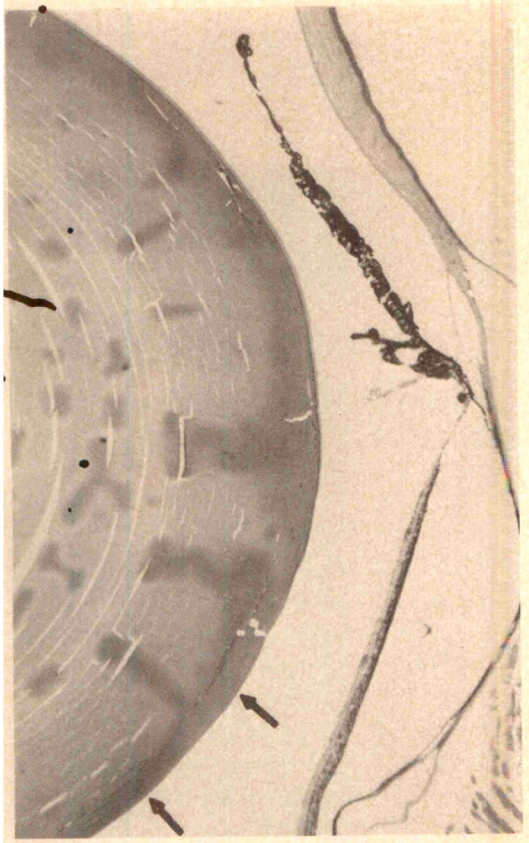


Fig. 10 (Burns and Feeney). Adult with hazy lens by slit lamp. Nuclei lie in several clusters at abnormally posterior subcapsular sites (arrows) (paraffin, hematoxylin and eosin, ×38).

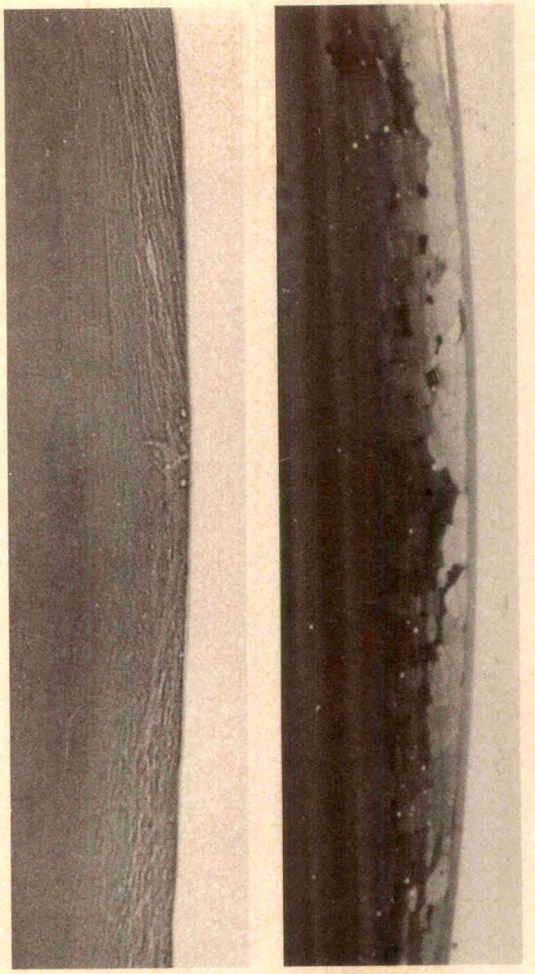


Fig. 11 (Burns and Feeney). Left, Posterior suture area of same lens as in Figure 10 (paraffin, hematoxylin and eosin, ×250). Right, Posterior suture area of fellow lens embedded in plastic. Note irregularities of superficial cells and various densities of deeper cells (plastic, toluidine blue, ×250).

opacities developed, the rest of the lens was obscured, and slit-lamp assessment of other abnormalities in these eyes was impossible.

After cataracts developed in the superficial cortex, either anteriorly or posteriorly, the lens nuclei disappeared with development of a total cataract (Fig. 15). Wrinkling of the capsule, causing a smaller lens, presumably resulted from a loss of protein through the lens capsule (Fig. 15). Inflammation in either the anterior or posterior chambers of the eye occasionally occurred, with attraction of macrophages (Fig. 15, bottom), that eventually transformed into fibrocytes. Iris atrophy and retinal detachment occasionally en-

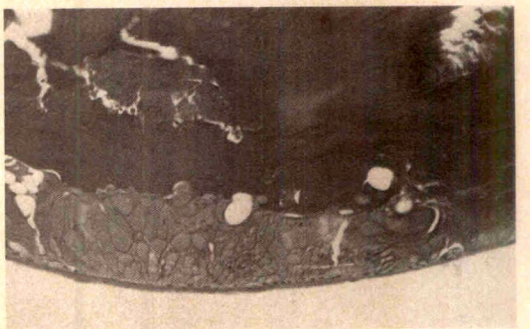
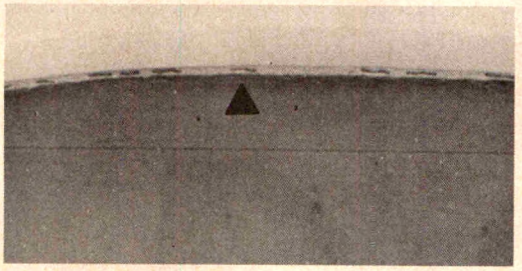


Fig. 12 (Burns and Feeney). Posterior subcapsular cataract. Note epithelioid cells (paraffin, hematoxylin and eosin ×42).





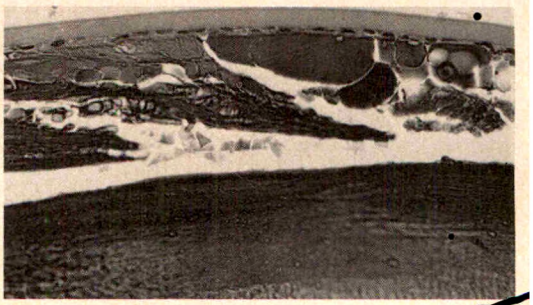


Fig. 14 (Burns and Feeney). Anterior cortical cataract (paraffin, hematoxylin and eosin, ×38).

sued, as observed in human hypermature cataract.

Discussion

Although there are many ways to produce experimental cataracts, "none of these has yet offered a definite clue to the intimate mechanism involved in the occurrence of the usual lenticular opacities in man."[6] Spontaneously developing cataracts provide an opportunity to study the biochemical and morphologic sequence of events leading to opacification.

Hereditary cataracts in the house mouse (*Mus musculus*) have been described.[7] These cataracts are visible by the 25th postnatal day and may be detected histologically in prenatal lenses. Various defects in the morphogenesis and maturation of the lens cells have been described in mice. In the Fraser cataract strain, abnormalities in cells of the invaginating lens vesicle have been reported.[8] Many later steps in lens cell differentiation are also abnormal, such as irregularities in cellular elongation, leakage

Fig. 13 (Burns and Feeney). Top, Anterior surface of eye whose slit-lamp appearance is shown in Figure 3, left. Nuclei (arrow) are somewhat pyknotic and resemble those about to undergo dissolution in the lens bow as they are displaced deeper into lens cortex (plastic, toluidine blue, ×240). Bottom, Posterior subcapsular cataract. Irregularities produced by various depths of epithelioid cell plaques correspond to various densities of the cataract shown in Figure 3, left and center (paraffin, plastic, toluidine blue, ×480).

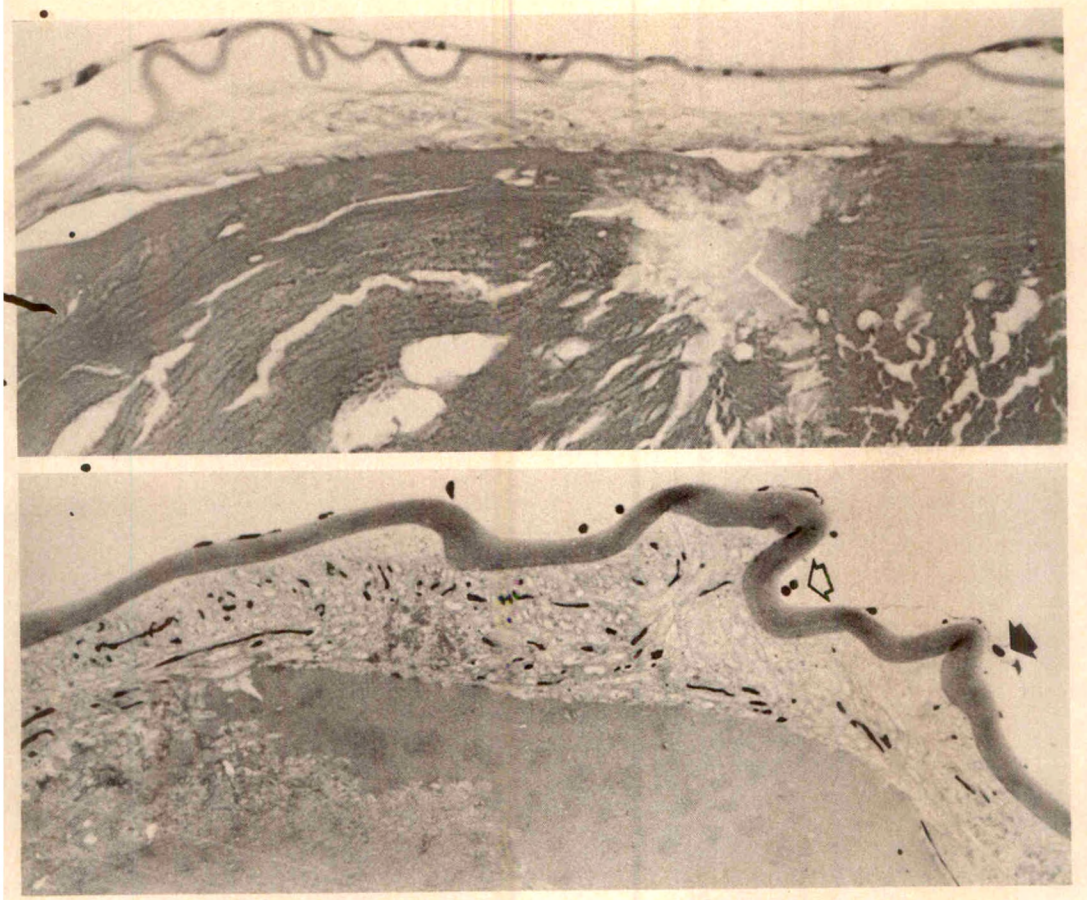


Fig. 15 (Burns and Feeney). Top, Hypermature cataract, right eye. Note the wrinkled capsule and acellular amorphous appearance of the cortical fibers (paraffin, hematoxylin and eosin, ×160). Bottom, Hypermature cataract, left eye. Toluidine blue-positive streaks in the cortex may be nuclear remnants. Note the macrophages (open arrow) outside the capsule apparently transforming into fibroblastic cells (solid arrow) (plastic, toluidine blue, ×130).

of nuclear material, persistence of nuclei, cellular necrosis, edema, and cell rupture. Abnormal proliferation of epithelial cells in this strain is secondary to early changes.[9]

In another strain of cataract-prone mice (Nakano, cross-bred with Charles River albino mice), the lens develops normally until the sixth postnatal day. Thereafter, swelling of the distal portion in the deep posterior suture area was observed along with abnormalities of denucleation.[7] Biochemical studies of these lenses indicated a deficiency of sodium-potassium activated adenosine triphosphate activity.[10] Inadequacy of the cation pump was responsible for the increased hydration of the lens cells and later cataract formation.

Cataracts in deer mice more closely resemble human senile lens opacities than most of the 12 types of experimental cataracts described by Duke-Elder.[6] Also, cataracts in deer mice resemble senile cataracts more than they resemble congenital or developmental cataracts (for example, late onset, cortical changes, opacities at the equator extending into the anterior and posterior cortex, and liquefaction). Perhaps these cataracts resemble most closely posterior subcapsular senile

cataract in that the opacity is confined to the zone immediately beneath the capsule (unlike secondary cataracts wherein the newformed lens fibers from the equator gradually crowd the posterior opacity forward so it lies within the cortex).[5]

The lens disease appears to occur after a considerable period of normal development of the lens. The cataract begins when equatorial epithelial cells, which are beginning to differentiate into the long lens "fibers" that stretch from the front to the back of the lens, begin to vacuolate. Subsequently or concurrently vacuoles also appear in the apical and basal poles of these ribbon-like cells.

Changes in the posterior lens cortical fibers cause epithelial cells at the equator to migrate backward. However, changes in anterior lens cortical fibers do not cause epithelial cells to migrate forward. This phenomenon has been observed in human cataracts for many years. Possibly the epithelial cells migrate posteriorly from the lens bow because of a demand for metabolic support, for example, to provide ion pumping in an area of fluid leakage. The anterior portions of the fibers are covered by the anterior epithelium and are therefore less vulnerable. Biochemical and morphologic analysis of differences in the two areas of the lens could be revealing in further study of cataract development. The mechanism by which epithelial cells migrate is under study in this laboratory.[11]

This paper is a preliminary report of a new, complex, and fascinating animal model of one of the commonest and costliest human diseases. It affords a high degree of predictability of onset of disease, since syndactyly occurs before cataract disease in lens cells. Some early morphologic abnormalities were observed by light microscopy. Electron microscopy and biochemical studies may reveal the critical anomaly in these lenses. With this model, we may study differences in anterior and posterior lens substances that might account for migration of equatorial cells posteriorly but not anteriorly.

Summary

A new type of hereditary cataract was predicted in the deer mouse (*Peromyscus maniculatus*) by the presence of syndactyly of the hind feet. Early morphologic changes were found in the equatorial cells that differentiated into new lens fibers. Later swelling at the anterior and posterior poles of these cells produced lens opacities. Anterior and posterior subcapsular cataracts progressed to a hypermature shrunken lens.

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CYSTOID MACULAR EDEMA ASSOCIATED WITH TOPICALLY APPLIED EPINEPHRINE IN APHAKIC EYES

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Baltimore, Maryland

Epinephrine maculopathy was described in 1967[1] as a reversible, toxic macular change occurring in aphakic eyes after the ocular instillation of topical epinephrine compounds. A later report[2] detailed its occurrence in 21 aphakic eyes and in one eye with a posteriorly luxed lens. The specific macular change appears to be edema, usually cystic, with or without tiny flame-shaped hemorrhages. To our knowledge, the flourescein angiographic features of this maculopathy have not been previously published.

Cystoid macular edema after cataract extraction (the Irvine-Gass syndrome) is a common maculopathy occurring in aphakic eyes and is not necessarily associated with use of topically applied epinephrine compounds.[3–5] Cystoid macular edema develops in 40 to 60% of eyes after cataract extraction[6–8] and is usually spontaneously self limited.[5] The flourescein angiographic appearance is characteristic.[4] Macular edema occurs most commonly during the first three months after cataract extraction, but we have observed its development, not associated with topically applied epinephrine, 20 years after surgery.

Fluorescein angiography has demonstrated that cystoid macular edema is a nonspecific, morphologic change associated with a variety of retinal vascular diseases, degenerative conditions, and intraocular inflammation, as well as following various types of ocular surgery (Table). The nonspecific nature of cystoid macular edema, its common occurrence in aphakic eyes, and the variable time of onset and unpredictable course make it difficult to be certain that cystoid macular edema is due to topically applied epinephrine in some cases.

We describe the course and fluorescein angiographic changes in an aphakic patient in whom instillation of topically applied epinephrine compounds repeatedly exacerbated cystoid macular edema in each eye.

CASE REPORT

This 69-year-old man developed open-angle glaucoma in 1958. In 1960, an iridencleisis was performed in each eye. These operations did not pro-

TABLE

CYSTOID MACULAR EDEMA DUE TO LEAKAGE FROM THE PERIFOVEAL CAPILLARY BED OF THE RETINA*

Retinal vascular disorders
Diabetic retinopathy
Hypertensive retinopathy, severe
Central retinal vein obstruction
Retinal branch vein obstruction
Retinal telangiectasis
Radiation retinopathy
Intraocular inflammation
Pars planitis
Behcet's syndrome
Acute nongranulomatous iridocyclitis[11]
Acute recurrent (nodular) cyclitis[11]
Sarcoidosis
Nematode endophthalmitis
Degenerations
Surface-wrinkling retinopathy
Retinitis pigmentosa (rare)
Senile "vitritis"[13]
Following ocular surgery
Cataract extraction
Penetrating keratoplasty (aphakic eyes)
Retinal reattachment[14]
Glaucoma filtering procedure
Pars plana vitrectomy

*A partial list of ocular conditions associated with this maculopathy.

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vide adequate filtration blebs, and the patient was again treated medically.

In 1967, the patient had markedly decreased vision in his right eye, and was initially seen by one of us (A.E.M.) in April 1968. At that time he was using his left eye for reading and was having difficulty because of early cataractous changes in the left eye and a restricted visual field due to glaucomatous optic atrophy. He was using 2% pilocarpine and epinephrine eyedrops in each eye and 500 mg of acetazolamide (Sequels) orally, every 12 hours.

Visual acuity was R.E.: 2/200, and L.E.: 20/50. A dense cataract was present in the right eye, and the left lens showed moderately severe posterior-subcapsular lens opacities. Intraocular pressure was 30 mm Hg in each eye by applanation tonometry. Gonioscopy showed the anterior-chamber angle to be open in each eye except where the iris pillars adhered to the iridencleisis sclerotomy sites. The right optic disk was not visible, and the left disk showed severe glaucomatous cupping. The coefficient of outflow was 0.20 in the right eye and 0.10 in the left eye. Perimetry studies showed glaucomatous field loss in each eye, with a nasal step in the right eye and marked peripheral constriction in the left eye with sparing of the central 20 degrees and the superotemporal quadrant (Fig. 1).

On April 11, one of us (A.E.M.) performed an intracapsular cataract extraction without complications in the right eye. Visual acuity was 20/20 two weeks later, and on Sept. 12, an intracapsular cataract extraction was performed without complications in the left eye. In an attempt to create postoperative filtering blebs, we used limbal-based conjuctival flaps, three buried 9-0 sutures, and light cautery to the edges of the limbal incision in each eye.[9] Three months after the second cataract operation, visual acuity was 20/20 in each eye. A filtering bleb was present in the left eye, and topically applied pilocarpine controlled intraocular pressure in the right eye. Sometime after surgery the anterior hyaloid face ruptured in the right eye, and a band of vitreous adhered to the limbal incision superiorly. The vitreous gel remained behind the iris plane in the left eye.

In September 1969, visual acuity was 20/25 in both eyes. We controlled intraocular pressure in the right eye with 4% pilocarpine eyedrops, every six hours. A filtering bleb was present in the left eye, and no medications were required. In July 1970, visual acuity in the left eye was 20/100 although the left macula appeared opthalmoscopically normal. Fluorescein angiography was not performed.

The intraocular pressure became more difficult to control in each eye, and progressive field loss developed in the right eye. In July 1971, pilocarpine eyedrops were discontinued in the right eye and 1/4% echothiophate iodide (Phospholine Iodide) and 1/2% epinephryl borate (Epinal) eyedrops were begun in each eye, every 12 hours. Intraocular pressure was approximately 30 mm Hg in the right eye, and in August 1971, 500 mg of acetazolamide was begun every 12 hours. The intraocular pressure was within normal limits during the next 18 months and there was no evidence of further visual field loss.

Visual acuity was R.E.: 20/20, and L.E.: 20/50 in November 1971. In June 1972, visual acuity was R.E.: 20/30, and L.E.: 20/80. In December 1972, visual acuity was R.E.: 20/60, and L.E.: 20/100. Intraocular pressure was R.E.: 21 mm Hg, and L.E.: 18 mm Hg. Cystoid edema was visible in the right macula when viewed with a Hruby lens. Fluorescein angiography showed severe cystoid macular edema in both eyes (Fig. 2). We considered epinephrine maculopathy and the patient was informed that topically applied epinephrine might cause cystoid macular edema but that this had not been definitely demonstrated. Because of the appreciable glaucomatous visual field loss and the difficulty in control-

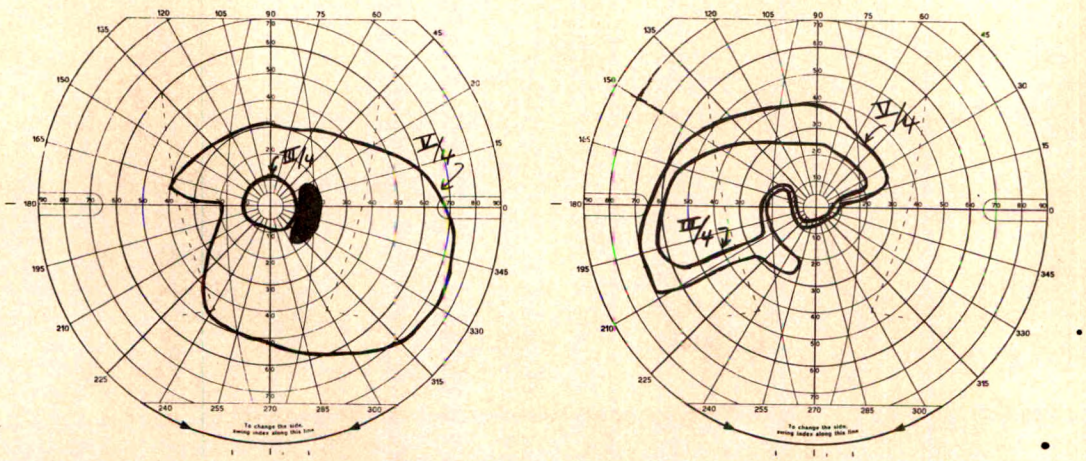


Fig. 1 (Michels and Maumenee). Perimetry studies done on April 31, 1968, showing glaucomatous field damage in each eye with severe field loss in the left eye (right).

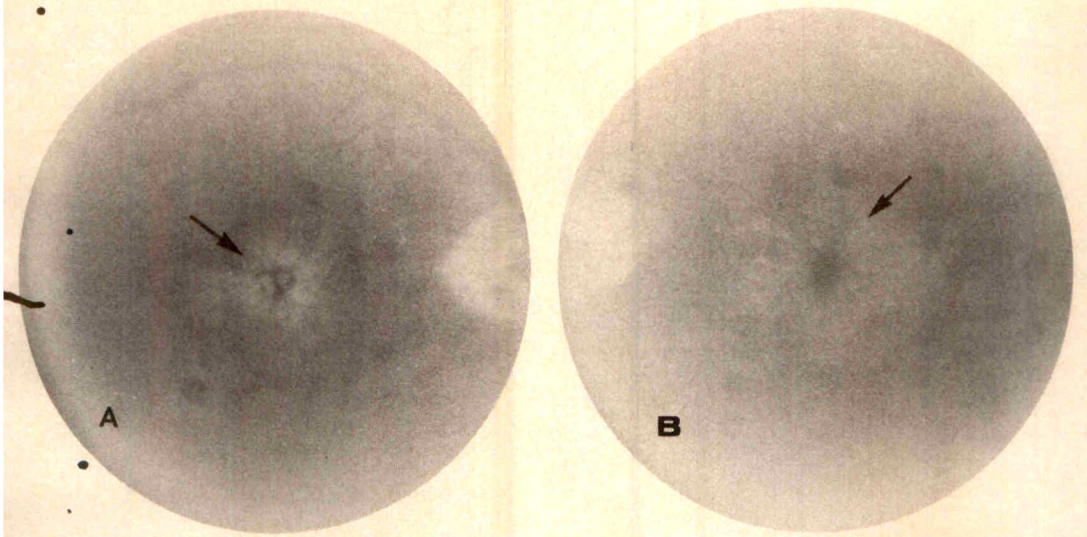


Fig. 2 (Michels and Maumenee). Late frames from fluorescein angiogram done Dec. 14, 1972, showing marked cystoid macular edema (arrows) in both eyes (A, 432 seconds; B, 507 seconds). Patient had used epinephrine eyedrops in both eyes for 18 months.

ling intraocular pressure, we suggested alternately discontinuing epinephrine therapy and later resuming it in each eye to determine whether the medication was contributing to the macular edema, and whether the medication was necessary to control the pressure and prevent further glaucomatous damage. On Jan. 19, 1973, the 1% epinephryl borate eyedrops were discontinued in the right eye. (The 1/4% echothiophate iodide eyedrops in both eyes and 1% epinephryl borate eyedrops in the left eye were continued.)

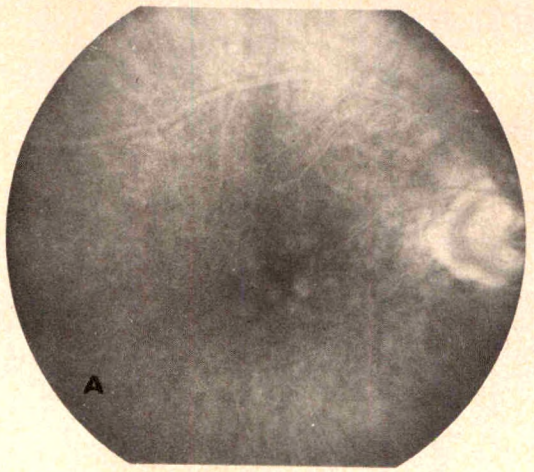
On Feb. 2, 14 days after discontinuing the epinephrine eyedrops in the right eye, visual acuity was R.E.: 20/25, and L.E.: 20/60. Fluorescein angiography again demonstrated cystoid macular edema in both eyes, with leakage from the perifoveal capillary bed of the retina (Fig. 3). However, the right eye showed less leakage and less accumulation of fluorescein than the left eye. One percent epinephryl borate eyedrops were begun, every 12 hours, in the right eye and discontinued in the left eye.

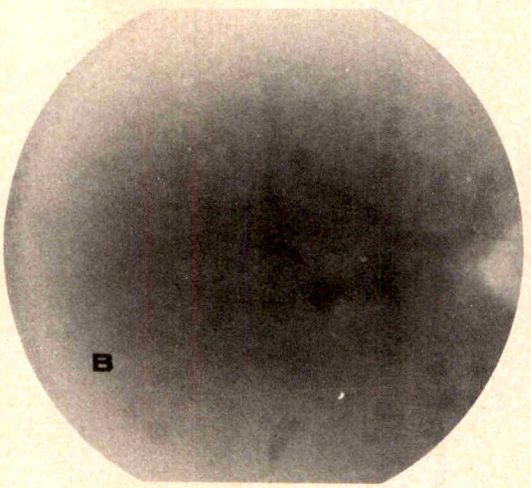
On Feb. 28, 26 days after resuming epinephrine eyedrops in the right eye and discontinuing these eyedrops in the left eye, visual acuity was 20/50 in both eyes. Fluorescein angiography showed markedly increased leakage from the perifoveal capillary bed in the right eye and increased cystoid macular edema, compared to the angiogram on Feb. 2 (Fig. 4). Prominent cystoid macular edema was also present in the left eye. The epinephrine eyedrops were discontinued in the right eye.

On April 4, five weeks after discontinuing epinephrine eyedrops in the right eye and nine weeks after discontinuing epinephrine in the left eye, visual acuity was 20/40 in both eyes. Fluorescein angiography demonstrated mild leakage from the perifoveal capillaries in both eyes and mild cystoid macular edema (Fig. 5). There was less fluorescein leakage and cystoid edema than five weeks earlier, especially in the right eye. On May 4, visual acuity was R.E.: 20/20, and L.E.: 20/25. (Epinephrine eyedrops had not been applied for nine weeks in the right eye and 13 weeks in the left eye). Intraocular pressure was R.E.: 22 mm Hg, and L.E.: 20 mm Hg. Two percent epinephrine hydrochloride eyedrops were begun in the right eye, every 12 hours. Fluorescein angiography was not performed. On May 18, 13 days after resuming epinephrine eyedrops in the right eye, visual acuity was 20/25 in both eyes. The right eye was moderately injected and we discontinued the epinephrine eyedrops. Fluorescein angiography was of poor quality, and we could not evaluate the amount of capillary leakage. Late frames of the angiogram showed moderate macular edema in the right eye and virtually no edema in the left macula (Fig. 6).

On June 15, 1% epinephryl borate eyedrops were started in the right eye, every 12 hours, because the intraocular pressure was elevated. Fluorescein angiography was not performed. On July 11, visual acuity was R.E.: 20/30, and L.E.: 20/25. One percent epinephryl borate eyedrops were discontinued in the right eye and started, every 12 hours, in the left eye.

On Aug. 29, six weeks after resuming topically applied epinephrine in the left eye and discontinuing epinephrine in the right eye, visual acuity was R.E.: 20/30, and L.E.: 20/80. Fluorescein angiography demonstrated marked leakage from the perifoveal capillaries in the left eye and prominent cystoid macular edema (Fig. 7). Considerable macular edema was also present in the right eye, although epinephrine eyedrops had not been applied for six weeks. Epinephrine eyedrops were discontinued in the left eye.





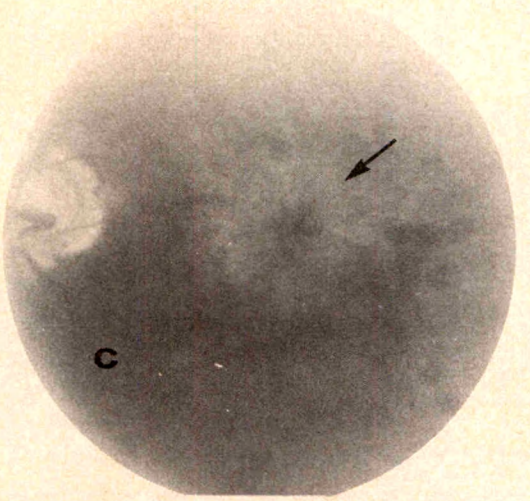
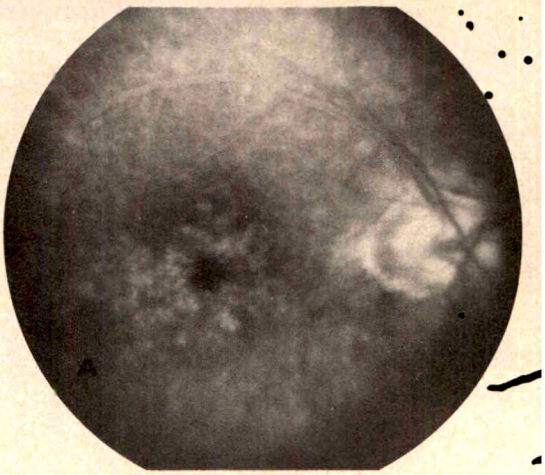
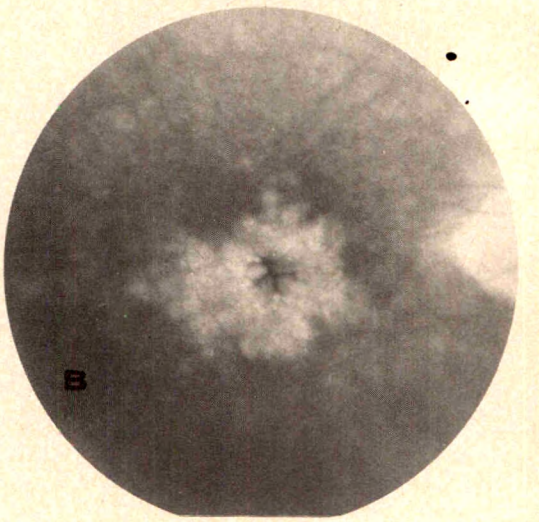


Fig. 3 (Michels and Maumenee). Angiogram done on Feb. 2, 1973 (14 days after discontinuing epinephrine eyedrops in the right eye), showing a marked decrease in cystoid macular edema (arrow) in the right eye (A, 110 seconds; B, 436 seconds)





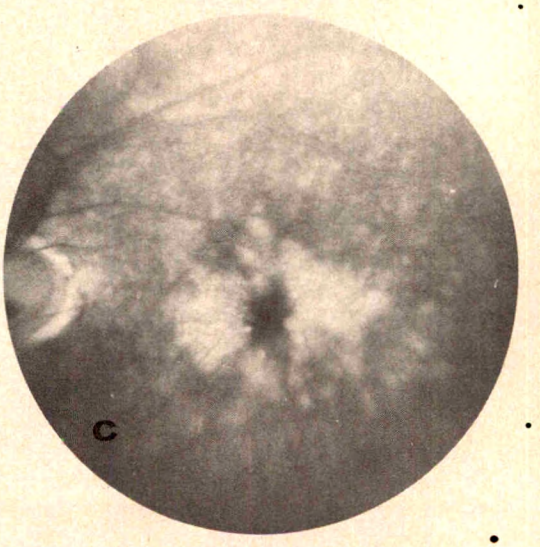
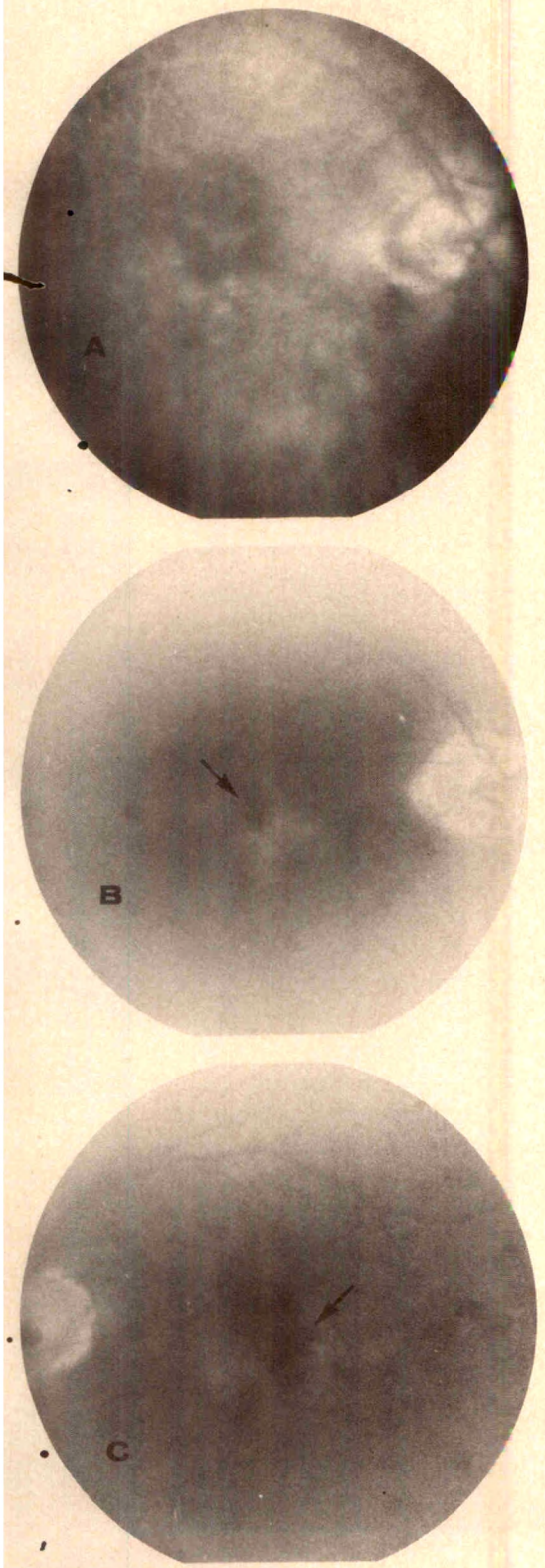


Fig. 4 (Michels and Maumenee). Angiogram done on Feb. 28, 1973 (26 days after resuming topically applied epinephrine in the right eye), showing increased cystoid macular edema in the right eye (A, 77 seconds; B, 335 seconds) compared to Figure 2. Prominent macular edema persists in the left eye (C,



On Oct. 31, 3½ months after discontinuing epinephrine eyedrops in the right eye and two months after discontinuing epinephrine in the left eye, visual acuity was 20/30 in the right eye and 20/25 in the left eye. Fluorescein angiography showed minimal leakage in the right macula and virtually no leakage in the left macula (Fig. 8). Topically applied epinephrine was not resumed, and on Jan. 30, 1974, visual acuity was R.E.: 20/15, and L.E.: 20/20. Fluorescein angiography again showed minimal leakage in the right macula and no leakage in the left eye (Fig. 9). Therapy with 1% epinephryl borate eyedrops was started in the left eye, every 12 hours.

On May 1, 1974, three months after resuming epinephrine eyedrops in the left eye, visual acuity was R.E.: 20/25, and L.E.: 20/40. Fluorescein angiography demonstrated marked leakage from the perifoveal capillary bed in the left eye and prominent cystoid macular edema (Fig. 10). Mild edema was also present in the right macula. The epinephrine eyedrops were discontinued in the left eye and resumed, every 12 hours, in the right eye.

On July 24, three months after resuming epinephrine eyedrops in the right eye and discontinuing epinephrine in the left eye, visual acuity was R.E.: 20/30, and L.E.: 20/25. Fluorescein angiography showed prominent cystoid macular edema in the right eye and minimal fluorescein leakage in the left macula (Fig. 11). Topically applied epinephrine was discontinued in the right eye.

On Nov. 22, visual acuity was R.E.: 20/40, and L.E.: 20/30. Intraocular pressure was R.E.: 18 mm Hg, and L.E.: 13 mm Hg. Visual fields for glaucomatous effects showed little change during the six-year interval since 1968. Fluorescein angiography demonstrated only mild cystoid macular edema in the right eye and little edema in the left eye (Fig. 12).

DISCUSSION

Cystoid edema occurs in the macular area in many ocular conditions (Table). The tangential orientation of the outer plexiform layer surrounding the foveola provides potential space for accumulation of considerable extracellular fluid. Fluid leaking from the perifoveal capillary bed of the retina accumulates within the outer plexiform layer in cyst-like spaces. Fluo-

Fig. 5 (Michels and Maumenee). Fluorescein angiogram done on April 4, 1973 (five weeks after discontinuing epinephrine eyedrops in the right eye and nine weeks after discontinuing epinephrine in the left eye), showing decreased cystoid macular edema (arrows) in the right eye (A, 75 seconds; B, 387 seconds) and in the left eye (C, 401 seconds) compared with Figure 3.

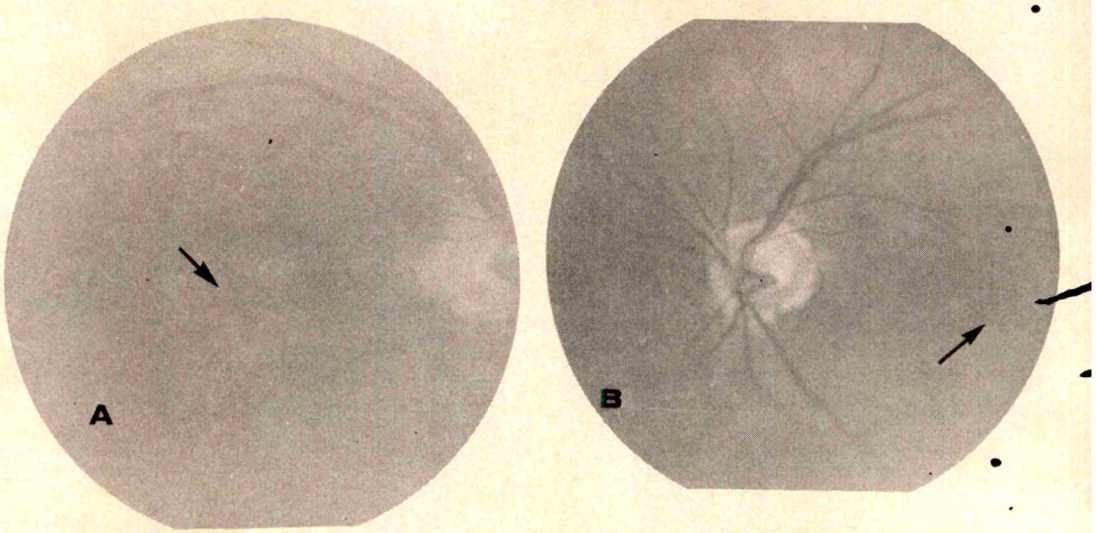


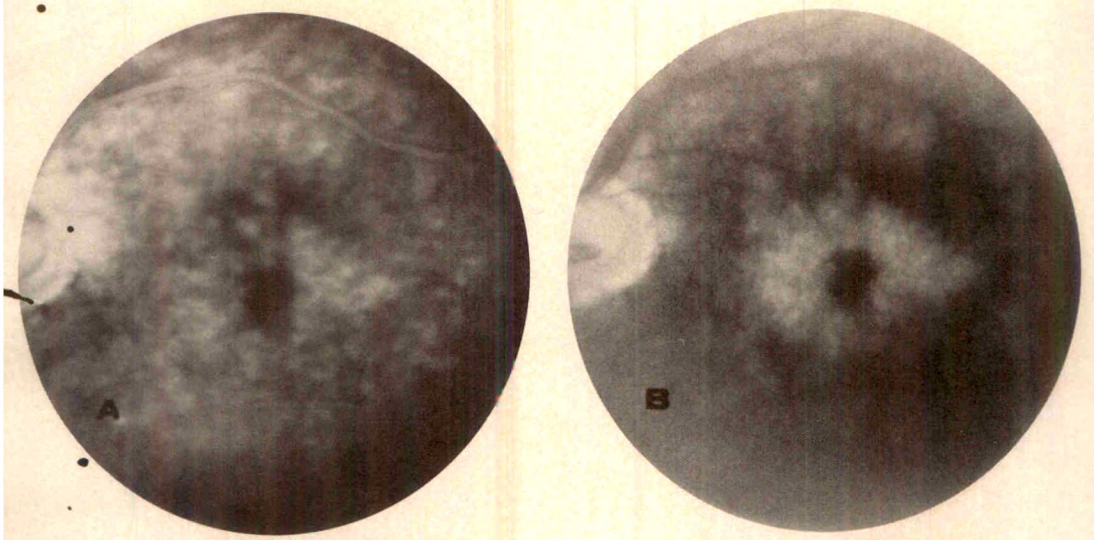
Fig. 6 (Michels and Maumenee). Fluorescein angiogram from May 18, 1973 (13 days after resuming epinephrine eyedrops in the right eye), showing moderate cystoid macular edema (arrow) in the right eye (A, 935 seconds) and little edema (arrow) in the left macula (B, 921 seconds).

rescein angiography demonstrates the site and severity of leakage and the amount of cystoid edema present.

The clinical and fluorescein angiographic features of cystoid macular edema observed in this patient cannot be distinguished from those seen in other conditions, including the Irvine-Gass syndrome. However, fluorescein angiography demonstrated repeated exacerbations associated with topically applied epinephrine and decrease of leakage when epinephrine eyedrops were discontinued. To our knowledge this is the first description in which the nature of the macular change, and the effect of topically applied epinephrine, have been documented by repeated fluorescein angiography. Possibly, unrecognized cystoid macular edema was present in the left eye before the use of topically applied epinephrine, but leakage was clearly influenced by the application or withdrawal of the drug. We studied three other patients in whom epinephrine seemed to reproducibly exacerbate cystoid macular edema in aphakic eyes. In these patients identical fluorescein angiographic features were demonstrated, but the response to discontinuing epinephrine was not as striking as in this patient.

The mechanism causing increased permeability of the perifoveal capillaries and the accumulation of extracellular fluid is not known. Direct vitreous traction on the macula does not seem to be necessary, and vitreous attachment to the macula is rarely observed in eyes with cystoid macular edema after cataract extraction.[4,5] The occurrence of cystoid macular edema in many ocular conditions suggests that the normal permeability characteristics of the perifoveal capillary bed are easily disturbed. Aphakic eyes have increased cystoid macular edema,[6,8,10] and they often show some irritation and intraocular inflammation when edema is present. Previously, we speculated that cystoid edema after cataract extraction arose because of a nonspecific, indirect vascular response to inflammation involving the anterior uveal tract—especially the ciliary body.[11,12] Epinephrine may act in a nonspecific fashion, initiating capillary leakage in certain susceptible aphakic eyes.

The original reports of epinephrine ma-



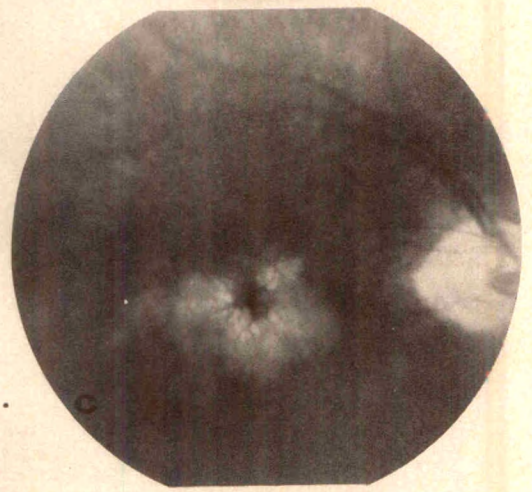


Fig. 7 (Michels and Maumenee). Fluorescein angiogram from Aug. 29, 1973 (six weeks after renewing topically applied epinephrine in the left eye and discontinuing epinephrine in the right eye), showing more leakage with increased cystoid macular edema in the left eye (A, 67 seconds; B, 526 seconds) compared with Figure 5. Moderate cystoid edema persists in the right macula (C, 541 seconds).

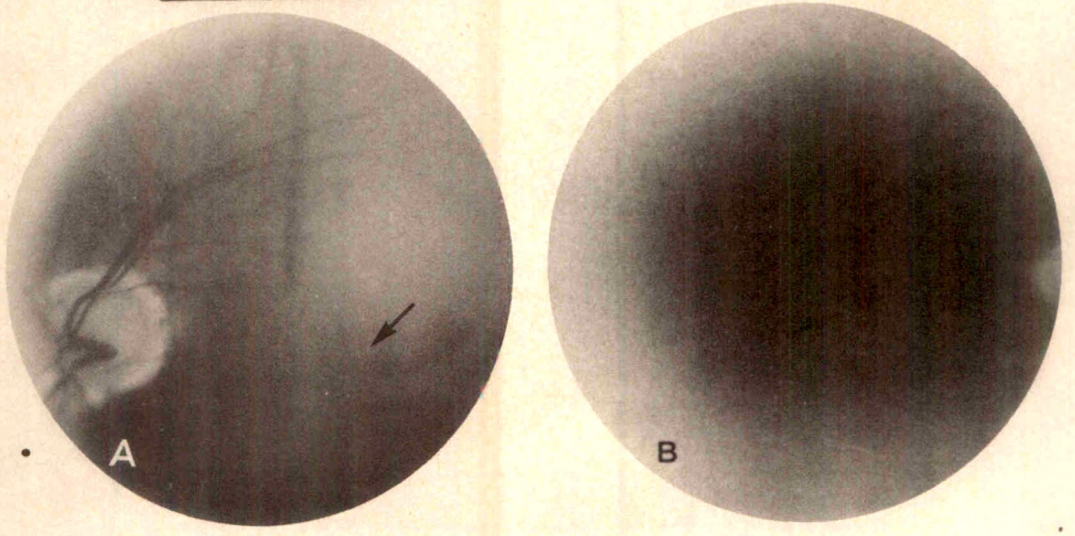


Fig. 8 (Michels and Maumenee). Fluorescein angiogram from Oct. 31, 1973 (3½ months after discontinuing epinephrine eyedrops in the right eye and two months after discontinuing epinephrine in the left eye), showing little leakage or macular edema (arrow) in the left eye (A, 415 seconds). Mild cystoid macular edema

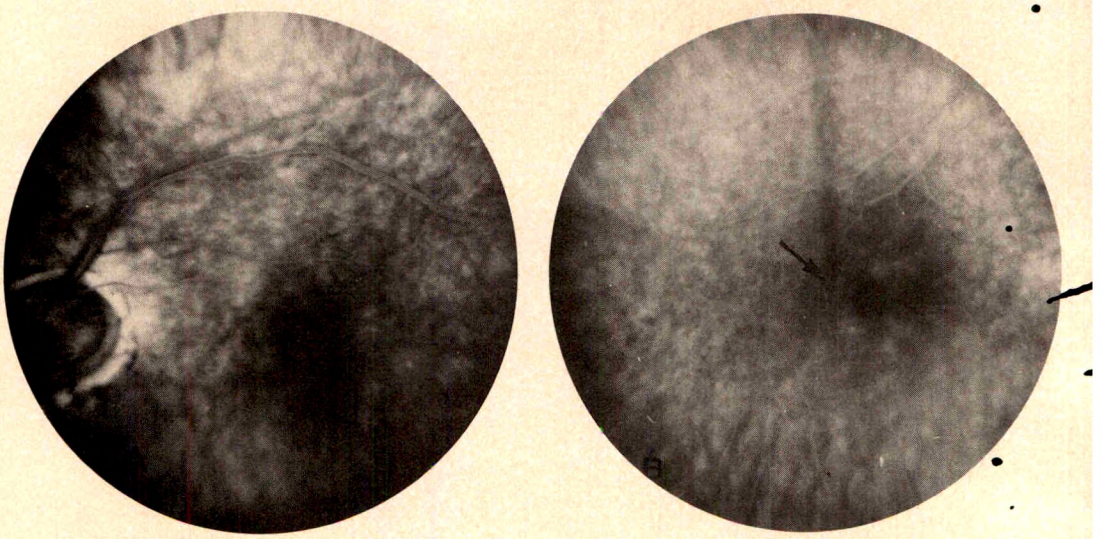


Fig. 9 (Michels and Maumenee). Late frames from fluorescein angiogram done Jan. 30, 1974 (6½ months after discontinuing epinephrine in the right eye and five months after discontinuing epinephrine in the left eye), showing little edema in the left macula (A), and only minimal leakage (arrow) in the right macula (B).

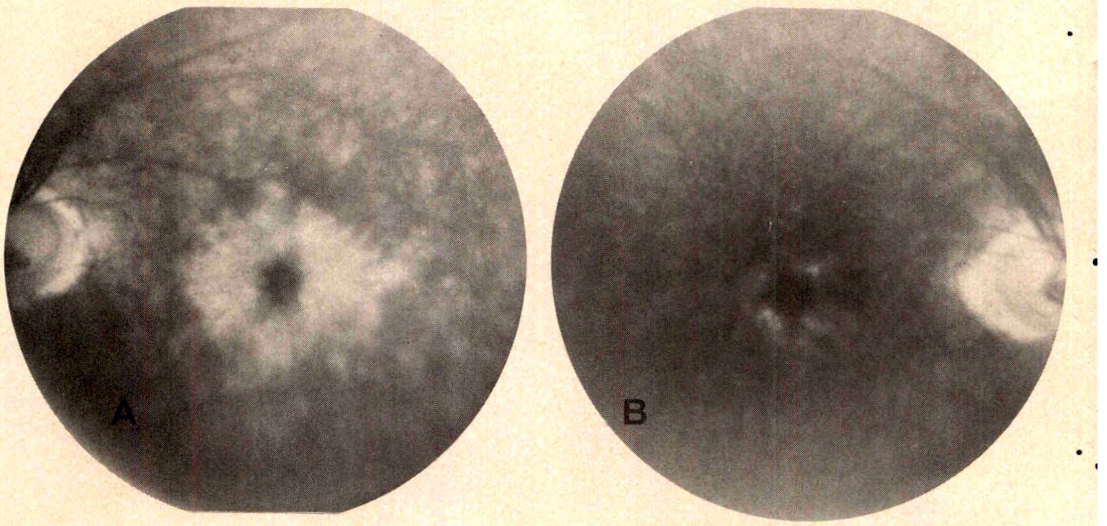
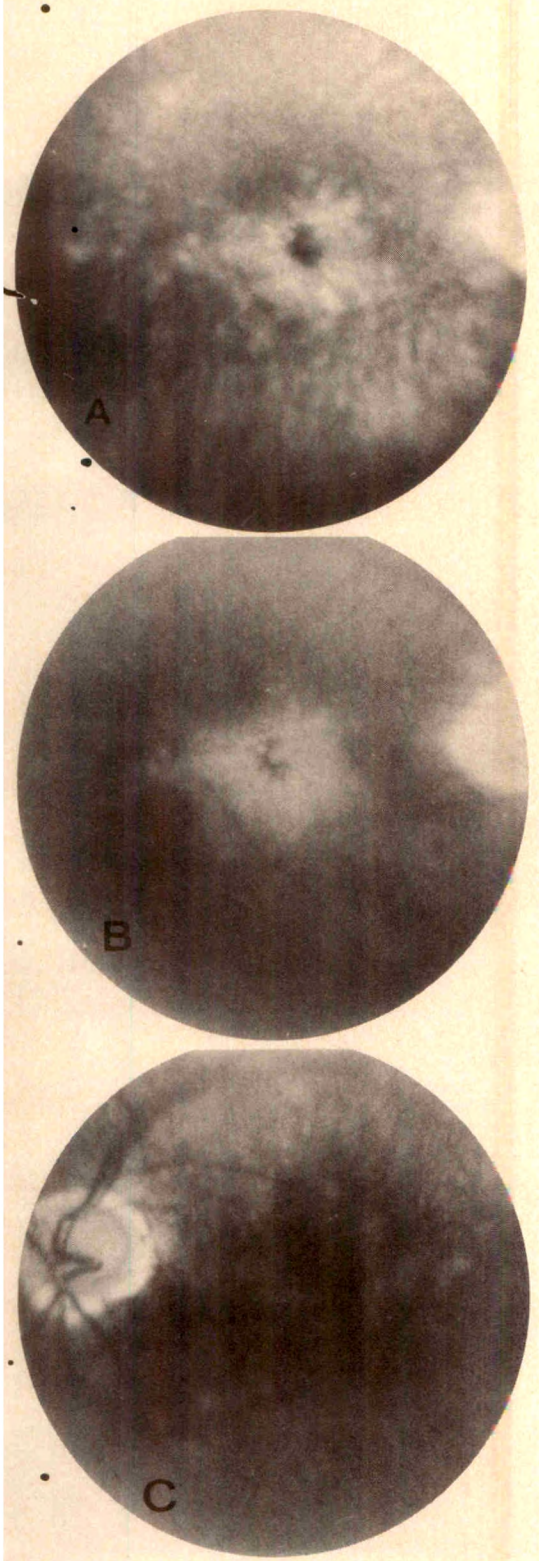


Fig. 10 (Michels and Maumenee). Fluorescein angiogram from May 1, 1974 (three months after resuming epinephrine eyedrops in the left eye), showing increased cystoid macular edema in the left eye (A, 438 seconds) compared with Figure 8. Mild edema is present in the right macula (B, 455 seconds).



culopathy described decreased vision and subtle ophthalmoscopic macular changes. Our patient had decreased vision during episodes of cystoid edema and improved vision when the edema subsided. However, vision may be minimally affected by the presence of macular edema, and the cystoid changes may be difficult to see if the vitreous cavity is somewhat cloudy. Fluorescein angiography is useful in confirming the presence of cystoid edema and comparing the amount of capillary leakage from time to time.

Previously in epinephrine maculopathy, fluorescein angiography was performed in two of the reported eyes.[2] Both eyes showed "early staining of the small parafoveal cyst but little diffuse staining of the macula." Our case demonstrates the usual angiographic characteristics of cystoid macular edema. Despite this difference, epinephrine maculopathy may represent the occurrence of otherwise nonspecific cystoid macular edema in certain susceptible aphakic eyes, initiated (or aggravated) by use of topically applied epinephrine compounds.

SUMMARY

A 69-year-old man with bilateral open-angle glaucoma and nonfiltering iridencleisis scars underwent combined cataract extraction and glaucoma filtering operations in each eye. Later, he again required intensive medical therapy including topically applied echothiophate iodide, epinephrine, and acetazolamide to control his glaucoma. Topical instillation of epinephrine repeatedly resulted in re-

Fig. 11 (Michels and Maumenee). Fluorescein angiogram from July 24, 1974 (three months after discontinuing epinephrine eyedrops in the left eye and resuming epinephrine eyedrops in the right eye), showing increased leakage in the right macula (A, 223 seconds; B, 815 seconds) with much cystoid macular edema compared with Figure 9. The left macula (C, 797 seconds) now shows minimal cystoid edema.

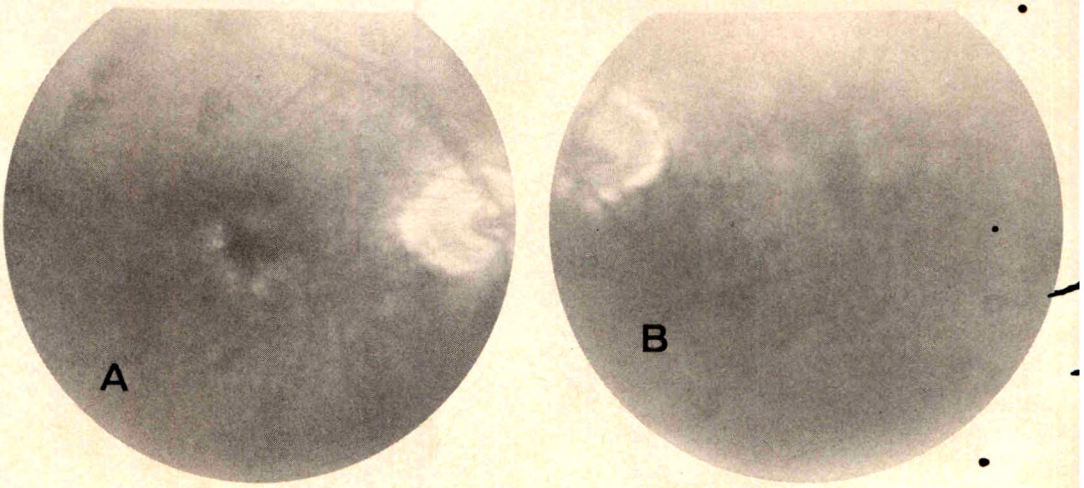


Fig. 12 (Michels and Maumenee). Fluorescein angiogram from Nov. 22, 1974 (four months after discontinuing epinephrine eyedrops in the right eye and seven months after discontinuing epinephrine eyedrops in the left eye), showing only mild cystoid macular edema in the right eye (A, 591 seconds) and little edema in the left macula (B, 600 seconds).

versible cystoid macular edema in each eye. The macular changes were documented by fluorescein angiography. The clinical and angiographic features of the macular edema in this patient did not differ from cystoid macular edema seen in other ocular conditions.

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OCULAR MELANOCYTOSIS AND MELANOMA

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Ocular melanocytosis or melanosis oculi is a congenital hyperpigmentation of the uveal tract and of the episclera. It is an unusual, but not infrequent, anomaly that is generally unilateral, producing a striking heterochromia. This ocular condition may be accompanied by a blue nevus in the innervation area of the first branch of the trigeminal nerve (nevus of Ota). The condition is stationary although the pigmentation may increase during pregnancy and with age.

It has been claimed that eyes with this anomaly are prone to develop melanomas. If this hypothesis is true, a close follow-up of all patients with melanosis oculi seems warranted. The darker eye should undergo a careful ophthalmoscopic examination under optimal conditions (dilated pupil, indirect binocular ophthalmoscope, and scleral indentation) every year or so.

It seems appropriate to review the evidence usually cited that this hypothesis is correct and that melanomas often occur in eyes with melanocytosis.

1. Many published cases of congenital melanosis also harbor a melanoma.

The data vary. Most authors quote an incidence of 25 to 29%.[1,2] If this were correct more than one fourth of the eyes with melanocytosis would develop a malignant tumor. This condition could then be regarded "as a real danger"[3] and "its prognosis should be viewed with some anxiety."[3] Another author advised the removal of all pigmented spots on these eyes.[2]

How this figure was arrived at is difficult to determine. An old statistic cites seven malignant tumors among 76 eyes with melanosis (less than 10%),[3] but this includes extraocular melanomas. The most complete survey[4] cites 14 malignant tumors among 110 eyes with melanocytosis. There were, however, only six choroidal melanomas (an incidence of more than 5%). The other melanomas originated in the conjunctiva, sclera, optic nerve, episclera, and orbit. As there is usually no conjunctival (only episcleral) hyperpigmentation, the epibulbar melanomas may have been secondary to an acquired melanosis (a condition previously not differentiated from melanocytosis) and not at all connected with congenital melanosis.

2. A melanoma has never been found in the normal eye when the fellow eye showed ocular melanosis. No such case has been reported and this is a powerful argument for the propensity of this pigmentary anomaly to degenerate into a malignant lesion.

The following arguments can be raised against the hypothesis that congenital melanosis is a precancerous condition:

1. The incidence of malignant tumors in such eyes has obviously been overreported. A melanoma of the choroid[5-7] may certainly develop in such an eye, but it is not frequent. Until 1958, 17 such cases were reported.[8] Recently, the occurrences of melanomas in the choroid,[9-12] iris,[13] and orbit[14-15] were reported in patients with the nevus of Ota, but these are unusual and may not present a trend.

Obviously, these are interesting cases, but they give us no clue as to the prevalence of this malignant degeneration. Only one report states that of ten patients with congenital melanosis, one developed a choroidal melanoma.[16] Nobody has followed prospectively a reasonable number

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of patients with ocular melanocytosis and determined how many would develop a melanoma.

2. In patients with bilateral ocular melanocytosis[17,18] or bilateral nevus of Ota,[19,20] the development of a unilateral choroidal melanoma is an obvious occurrence. If the hypothesis is true, a bilateral melanoma should occasionally develop in a patient with bilateral ocular hyperpigmentation. Such an incidence has not been reported.

3. Among patients with choroidal melanoma, only a few have an underlying congenital melanosis (three of 281).[21]

Case report

This 67-year-old white woman had always known her right eye appeared darker than her left eye, but it never bothered her. A dentist told her this was a potentially dangerous lesion and urged her to visit an ophthalmologist.

She was first seen here on March 12, 1962. Visual acuity was nearly 6/6 in both eyes. A deep, episcleral pigmentation was noticed in the right eye around the cornea (Fig. 1). No such pigmentation was noticed on the left eye (Fig. 2). The right iris was diffuse and yellow-brown, whereas the left iris was blue with two small freckles (Fig. 3). The pupils were round, equal, and reacted promptly. The right fundus appeared brownish, whereas the left fundus was orange.

A right ocular melanocytosis was diagnosed and fluorescein angiography was performed. Yearly follow-ups were advised because melanomas could develop in her right eye. The patient returned twice, but failed to return later since she had no real difficulties with her eyes.

On Jan. 10, 1974, the patient returned with a three-week history of loss of vision in the left eye. This loss was especially marked in the nasal field of the left eye. Visual acuity was R.E.: 6/6, and L.E.: 6/30 −1. A solid, massive retinal detachment was noted in the temporal aspect of the blue left eye (Fig. 4). Intraocular pressures were normal in both eyes. The pigmentary changes in the right eye were unchanged.

Fluorescein angiography revealed a pattern characteristic for choroidal melanoma in the left eye (Fig. 5). The echogram showed a highly vascularized, solid mass in the superior temporal quadrant of the left eye with a maximal prominence of 4.5 mm and low reflectivity (Fig. 6). The echogram was diagnostic for choroidal melanoma. On Jan. 16, using the radioactive phosphorus uptake test in the operating room, a count of 111-148 was obtained on the temporal side of the left eye compared to a count of 47 on the nasal side, 36 in the upper segment, and 51 in the lower segment. The left eye was enucleated.

This histologic examination revealed a choroidal melanoma of mixed cell type in the left eye. The retina was detached adjacent to the tumor. The pigment epithelium of the retina exhibited degenerative and proliferative changes over the tumor. The tumor did not extend through the sclera (Fig. 7).

This seems to be the first recorded case of a patient who developed a choroidal melanoma in the blue eye, while the fellow eye with the melanosis remained unchanged.

Discussion

The frequency of this condition is overestimated. While each ocular pathology laboratory has some eyes with melanoma associated with congenital melanosis, most of these cases have been collected at various meetings or were contributed as teaching slides. In our laboratory, we have three such eyes processed in Iowa, and 11 others processed in other cities but contributed to our collection. These three cases of choroidal melanoma associated with melanocytosis come from an unknown pool of patients with congenital melanosis.

Another way to show the statistical insignificance of the melanoma-melanocytosis association is to regard the entire pool of choroidal melanomas. During the last 30 years our laboratory has processed 418 eyes with choroidal melanomas. Of four patients with unilateral melanocytosis, in three of them the tumor developed in the darker eye (0.7%). In the fourth patient it developed in the blue eye (0.24%). This is statistically insignificant, if we assume that among Iowans[22] the incidence of hazel or brown eyes lies between 39 and 44% and that of light eyes between 56 and 61%.

Therefore, I have to agree with the opinion of the man, honored by this issue, who states, "but only rarely is there a development of a uveal melanoma" in such eyes.[23]

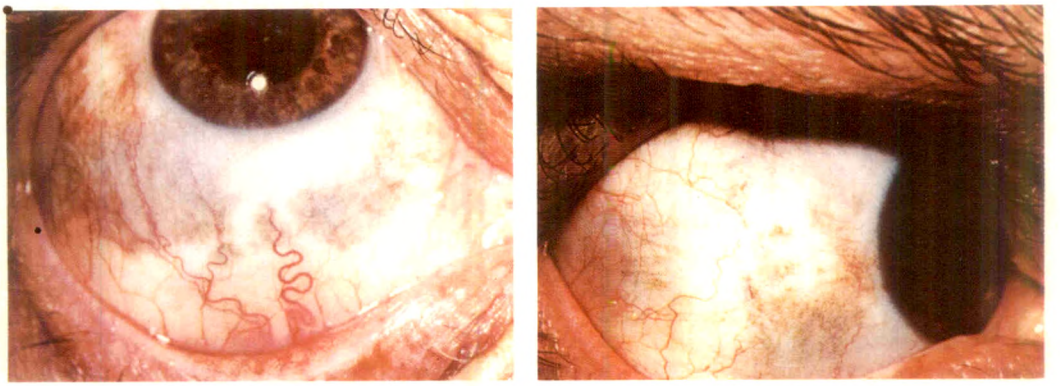


Fig. 1 (Blodi). The right eye with melanocytosis. There is deep scleral pigmentation and a deep brown iris. Left, looking up; right, looking to the left. Pictures taken in 1962.



Fig. 2 (Blodi). Heterochromia (melanocytosis on the right). Picture taken in 1974.

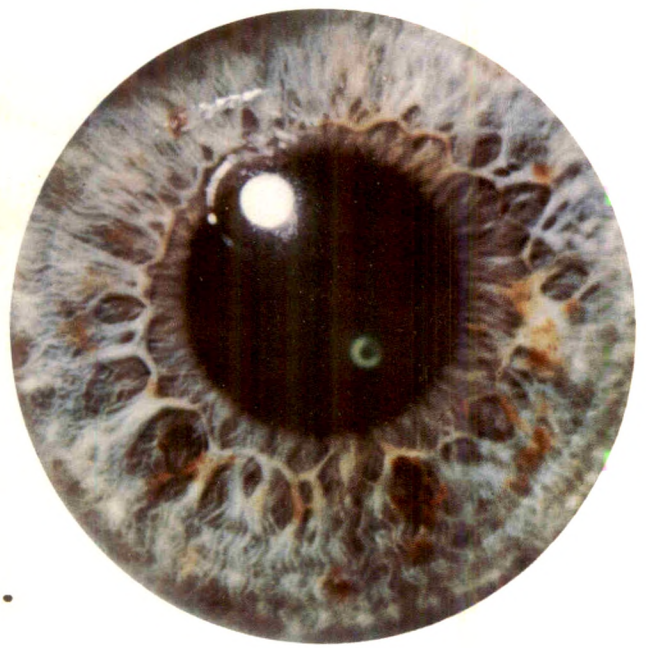


Fig. 3 (Blodi). The left blue iris. Picture taken in 1974.

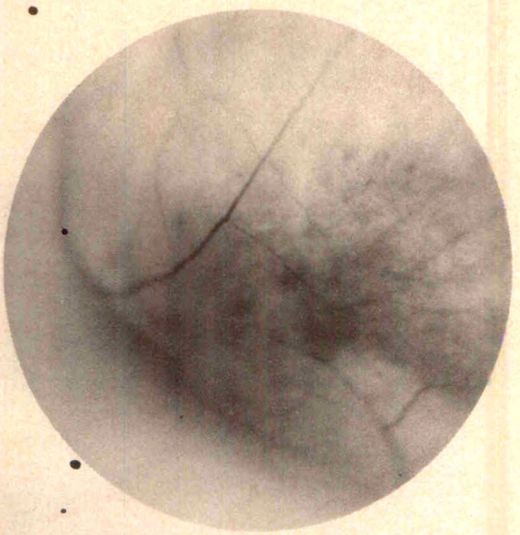


Fig. 4 (Blodi). Left eye has solid detachment.

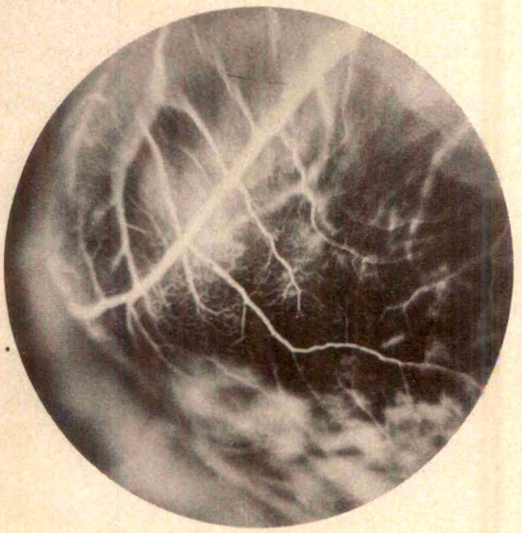
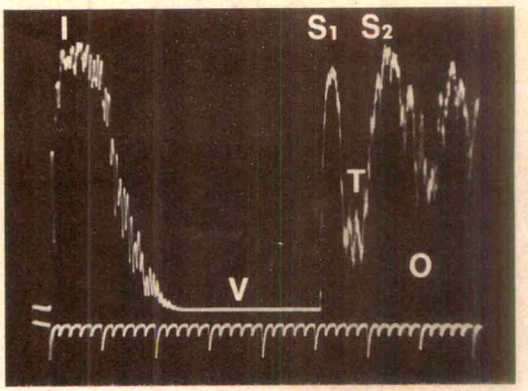
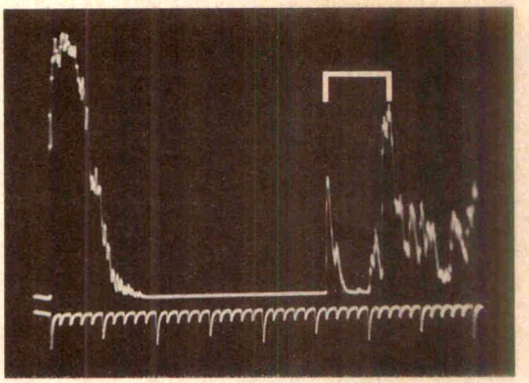


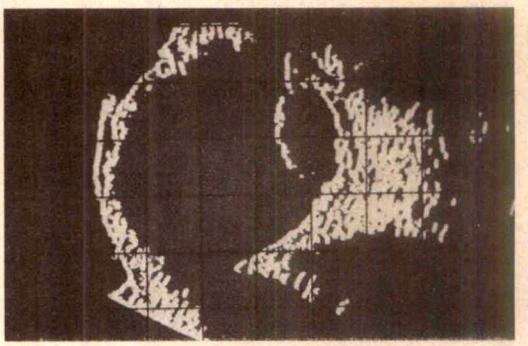
Fig. 5 (Blodi). The choroidal lesion, 20 seconds after the injection of the dye, shows the independent vascularization of the tumor.



A



B



C

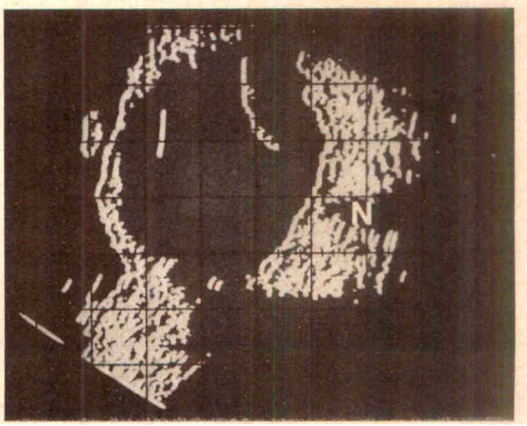


Fig. 6 (Blodi). A-scan (A and B) and B-scan (C and D) echograms from a solid, low-reflective, 4.5-mm prominent vascularized tumor in the upper temporal quadrant of the left eye. The A-scan patterns are pathognomonic for malignant melanoma. I indicates initial spike corresponding with the anterior ocular surface; V, baseline indicating clear vitreous body; S_1, surface spike from the retinal surface lining the tumor; T, tumor spikes (height and mobility as observed during the examination) are typical for melanoma; S_2, echo spike from the inner scleral surface = posterior tumor surface; and O, orbital signals. The B-scan echograms indicate the lateral extension of the melanoma (C) and its situation in regard to the optic nerve (N).

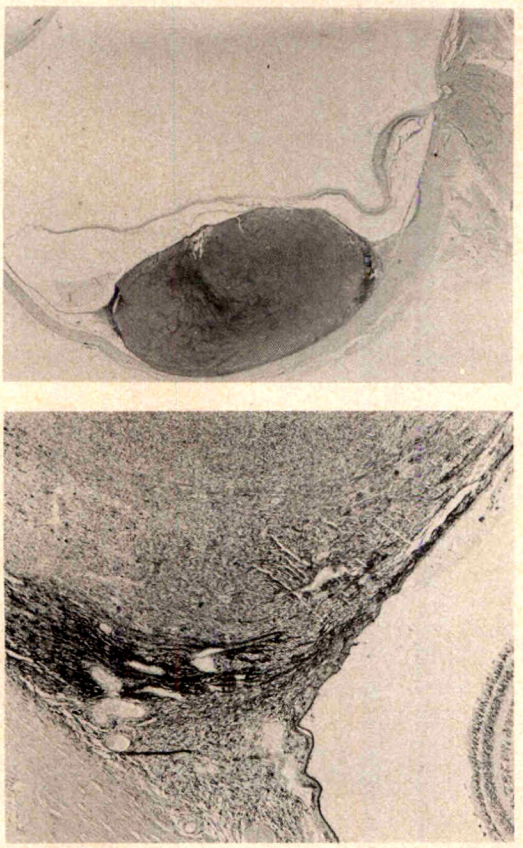


Fig. 7 (Blodi). The choroidal tumor. Top, Overall view of the melanoma (hematoxylin and eosin, ×4). Bottom, The margin of the neoplasm with retinal detachment (hematoxylin and eosin, ×40).

Summary

The hypothesis that ocular melanocytosis is a precancerous condition that may lead to a choroidal melanoma should be seriously questioned for the following reasons:

The incidence of malignant degeneration in a hyperpigmented eye is unknown and overreported.

If the hypothesis were correct a bilateral melanoma would occasionally occur in patients with bilateral melanosis. No such case has been reported.

In patients with unilateral melanosis the blue, unaffected eye may also develop a melanoma. A 67-year-old white woman with one dark and one blue eye provided the first such instance, although previous cases may not have been reported if their histologic picture was not unusual.

The incidence of melanoma in our patients with unilateral melanosis was rare compared with the many melanomas developing in normal pigmented eyes (4/418).

I found no statistically significant difference in the incidence of choroidal melanomas originating in the hyperpigmented or in the blue eye in patients with unilateral ocular melanocytosis.

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VASCULAR OCCLUSIONS IN THE EYE FROM CARDIAC MYXOMAS

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Soma Weiss once observed that a diagnosis was easy so long as one thought of it. The truth of this is especially poignant for occlusive vascular disease caused by cardiac myxomas. The diagnosis is easy to establish, and may be lifesaving, if one includes it in the etiologic differentiation. The present paper is based on the account of two patients in whom occlusion of the central retinal artery (and of the choroidal artery in one) was one of the signs of myxomatous emboli from the heart but the diagnosis was not included in the differentiation until after death in one case and only after a series of vascular accidents in the other case.

Cardiac myxomas comprise a well-recognized but infrequent tumor. The majority arise from the endocardium of the left atrium. They commonly project as polypoid masses into the cavity of the atrium and through the mitral valve into the ventricle. Histopathologically the tumors have distinctive stellate and angulated cells with abundant mucoid stroma. They grow slowly, one tumor took nine years to increase its diameter from 6 to 9 cm^2, and can now be successfully excised with bypass surgery. They occur at any age and in either sex.

The initial symptoms of cardiac myxomas may be confusingly protean. There may be simply evidence of cardiac congestion and pulmonary hypertension with cardiomegaly. Or the signs may suggest mitral stenosis. When fever, anemia, and elevated sedimentation rate are superimposed, subacute bacterial endocarditis is suspected. In such cases a negative history of prior rheumatic fever and negative blood cultures are most significant. The diagnosis is to be especially considered when the symptoms of pulmonary hypertension are disproportionately greater than the auscultatory signs.[1]

The tendency of cardiac myxomas to discharge embolic fragments into the arterial circulation is an important feature. Indeed, distal emboli frequently comprise the initial symptoms. Such patients present with vascular occlusions in the brain, eye, or limbs and the source of the emboli may be easily overlooked.

Retinal emboli from cardiac myxomas have been previously reported in eight patients. Jampol, Wong, and Albert[2] reviewed the six cases, including one of their own, reported up to early 1973. Since then two more cases have been described.[3,4] Seven of the eight cases had associated neurologic signs and seven had involvement of the left eye.[2]

The fundus picture in the eight cases was one of occlusion of the retinal artery but the embolus, or what could be interpreted as an embolus, was evident in one case only.[3] Choroidal lesions were also noted clinically in two cases.[4,5] Of the first six cases the diagnosis was made before death in only one. In the subsequent two cases the correct diagnosis was made and the patients were successfully treated.

Histopathologic studies of the eyes were carried out in three patients.[2,5,6] Not only had the retinal arteries been occluded in all three patients but the ciliary arteries were also plugged by myxomatous tissue. Emboli were also seen in the choroidal artery in one case.[2]

Findings in our two new cases confirm some of the previous observations and

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add several ophthalmologic features that have not been emphasized before. The radiologic and general pathologic features of both cases were previously reported.[7,8]

CASE REPORTS

Case 1—This 17-year-old boy had a history of malaise, night sweats, anorexia, weight loss, pains in the calves of his legs, and occasional red spots on his hands of several months' duration. The only significant finding on physical examination was a systolic murmur. The electrocardiogram was reported to be normal. No abnormality was noted in the eyes at this time. Sedimentation rate was 31 mm. Hemoglobin count was 9.5 g/100 ml.

A presumptive diagnosis was made of subacute bacterial endocarditis although the patient gave no history of rheumatic fever; repeated blood and bone marrow cultures were negative; and the rheumatoid factor was negative. The patient was treated with large doses of penicillin (36×10^6 units daily) and streptomycin (2 g daily).

While in the hospital, the patient became stuporous, aphasic, hemiplegic on the right side, and blind in the left eye. The fundus showed typical arterial occlusion with pale arteries and fragmentation of the blood column. A left carotid arteriogram revealed multiple obstructions in the small arteries compatible with embolization.

One month later the aphasia and hemiplegia had improved but the left eye remained blind. All the retinal arteries of this eye were extremely narrow or obliterated and heavily ensheathed (Fig. 1). At one point above the disk, the ensheathing extended beyond the artery (glial-like tissue). The nerve head was pale. Fluoroangiography at this stage showed delayed filling of the retinal vessels and extravascular staining along the superior and inferior retinal arteries at the sites of most conspicuous ensheathing (Fig. 2).

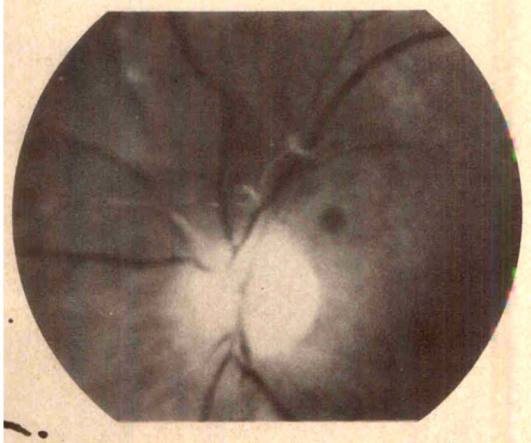


Fig. 1 (Cogan and Wray). Case 1. Fundus one month after occlusion of the retinal arteries showing arterial narrowing and conspicuous ensheathing.

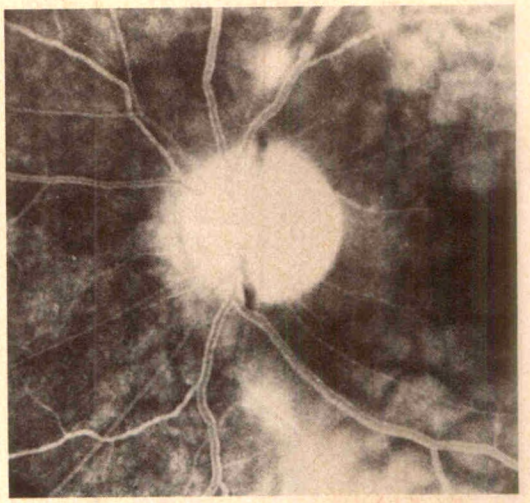


Fig. 2 (Cogan and Wray). Case 1. Fluoroangiography showing extravascular staining at the sites of ensheathing.

Shortly thereafter the patient suddenly developed numbness in the lateral aspects of both legs and the scrotum with severe pain in his thighs. No pulsations were palpable in his legs. Arteriography confirmed a saddle embolus and the patient underwent bilateral iliac artery exploration, which disclosed a myxoma. Three days later the myxoma was removed from the right atrium. Convalescence was uneventful except for occasional seizures, controlled by dilantin.

The patient developed transient ache in the left arm and shoulder 20 months after the initial examination. The right cardiac and pulmonary angiograms, however, were normal and the symptoms subsided without explanation. The left fundus showed narrowed vessels and optic atrophy (Fig. 3).

Case 2—This 20-year-old woman had the initial symptoms of sudden vertigo and diplopia. Examination revealed a left third-nerve paralysis with blepharoptosis and mydriasis. A saccular aneurysm was suspected but not found on arteriography. The presumed diagnosis was changed to multiple sclerosis and, for this reason, the patient elected to have her fallopian tubes ligated. The oculomotor paralysis cleared within a matter of weeks.

The patient came under observation again about one year later with an intervening history of paresthesias, numbness, and recent diplopia and collapse. Examination of the ocular motility revealed a typical right-sided internuclear ophthalmoplegia.

About this time, the patient complained of blackout spells. Ophthalmoscopy of the right eye showed two grayish areas above the right fovea, possibly corresponding to the distribution of a cilioretinal artery (Fig. 4), and a splinter hemorrhage on the

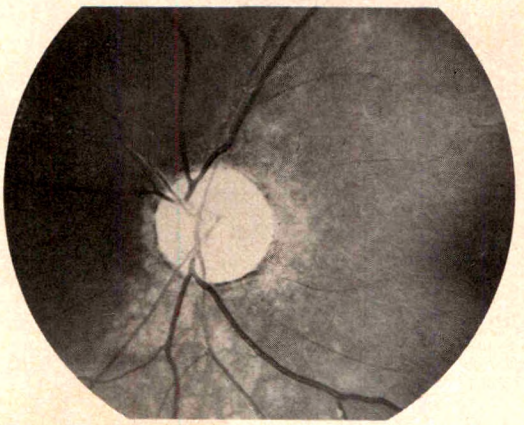


Fig. 3 (Cogan and Wray). Case 1. Fundus 20 months after the occlusion showing pallor of the disk and extreme narrowing of the arteries with little or no arterial opacification.

right disk. Visual fields showed a corresponding paracentral scotoma below the point of fixation. The ophthalmologic diagnoses were vascular occlusions in the brain stem and in the retina. No emboli were seen and fluoroangiography indicated normal flow without leaks. In addition several areas of chorioretinal degeneration were present in the periphery of both eyes (Fig. 5).

Arteriography of the carotid and vertebral systems showed multiple, diffuse aneurysms of the cerebral cortical arteries in both hemispheres. In retrospect these are thought to be characteristic of myxomatous emboli.[8] Biopsy specimens of the temporal artery and of the gastrocnemius muscle showed normal tissue only.

The patient developed a variety of signs and symptoms that included transient pain, swelling,

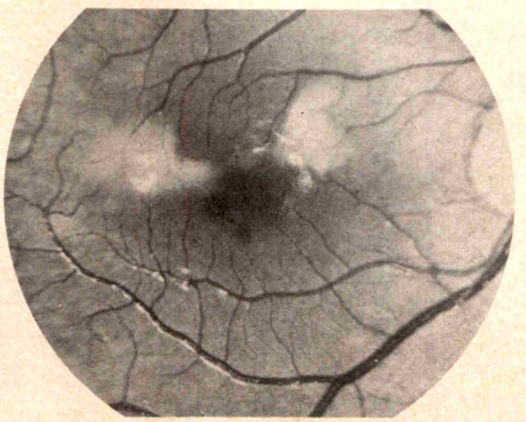


Fig. 4 (Cogan and Wray). Case 2. Fundus of right eye showing opacification of the retina above and to either side of the macula.

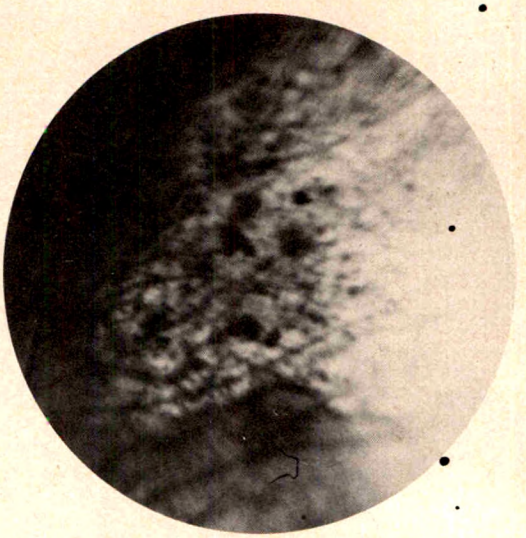


Fig. 5 (Cogan and Wray). Case 2. Focus of chorioretinal degeneration in periphery of right eye.

and purplish discoloration of one foot, and neurologic symptoms with left homonymous hemianopia and absence of the opticokinetic response on rotation of the field to the patient's right. A cardiac murmur was noted but interpreted as a papillary muscle dysfunction. Vaculitis was the assumed diagnosis.

Finally, the patient developed sudden vertigo, nausea, vomiting, stupor, seizures, and tetraplegia. The internuclear ophthalmoplegia was now bilateral and a right homonymous hemianopia was present. The left eye showed occlusion of the central artery with stasis in the veins and an opaque retina. The patient rapidly became unresponsive and died.

RESULTS

General autopsy indicated a myxoma of the left atrium with embolic infarction in most viscera and in the cerebrum, cerebellum, and brain stem.

Ocular histopathology—Both eyes were removed and found to have histopathologic abnormalities confined to the posterior halves of the globes.

The right eye showed: (1) chorioretinal changes in the nasal equatorial area corresponding to the pigmentary degeneration which had been seen clinically; (2) optic atrophy and secondary gliosis of the nasal half of the optic nerve; and (3) myxomatous emboli in some posterior ciliary vessels and in the choroid.

The chorioretinal degeneration in the

nasal periphery bridged the equator and occupied an area approximately 3 mm in diameter. It consisted of irregular clumping and attenuation of the pigment epithelium with thinning of the subadjacent choroid and loss of the photoreceptors in the overlying retina. Some pigmentary cells had migrated into the retina.

The atrophy and gliosis of the nasal side of the optic nerve were evident in low-power microscopic magnification (Fig. 6). The normal columnar arrangement of nerve fibers was replaced by hypercellular tissue consisting of astrocytes (Fig. 7). The ganglion cells were absent from the nasal retina.

The myxomatous emboli were most obvious in the ciliary arteries on the nasal side but were present in some arteries on the temporal side as well. The most conspicuously involved vessel was the artery inserting approximately 5 mm nasal to the nerve (Fig. 8). This artery was distended two to three times its normal diameter, enclosed in a thick adventitia, and filled with typical myxomatous tissue containing pleomorphic cells that varied from individual stellate patterns to a syncytium resembling epithelium. The abundant stroma had a typically loose matrix. This



Fig. 7 (Cogan and Wray). Case 2. Magnified view of optic nerve showing atrophy of fibers and gliosis on nasal (right) half (PAS, ×80).



Fig. 6 (Cogan and Wray). Case 2. Nerve head of right eye showing gliosis of optic nerve fibers and loss of ganglion cells and of retinal nerve fibers from the nasal (right) half (PAS, ×14).

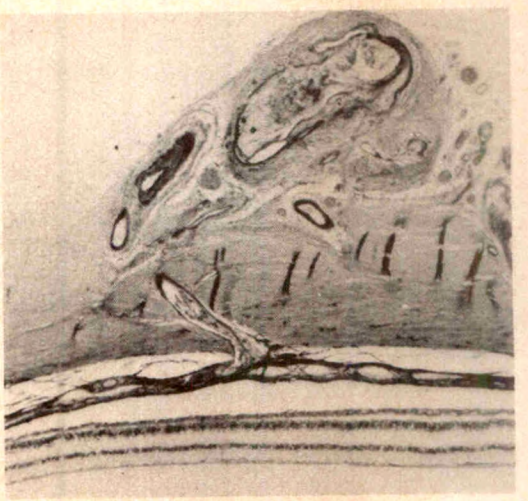


Fig. 8 (Cogan and Wray). Case 2. Posterior ciliary artery distended with myxomatous emboli approximately 5 mm nasal to the nerve head of the right eye. The embolus-filled artery can be traced through the sclera into the choroid (PAS, ×28).

embolus-filled vessel could be traced through the sclera into the choroid but promptly lost its myxomatous content. Similarly on the temporal side, beneath the macula, myxomatous emboli could be identified in the choroid close to the site of entry of the ciliary arteries. The emboli were most conspicuously demonstrated with Alcian blue stain (Fig. 9).

One of the posterior ciliary vessels on the nasal side was occluded by a hyaline substance in which the myxomatous tissue could scarcely be recognized (Fig. 10). This hyaline substance was abundant and stained by the PAS method, suggesting excessive basement membrane formation. It differed from mature collagen in showing no birefringence.

The left eye was the more severely involved. The anterior half of the globe including the peripheral retina was, however, normal. The posterior half showed: (1) total necrosis of the nerve head and extensive necrosis of the contiguous retina; and (2) myxomatous emboli in practically all the posterior ciliary arteries with extension into the choroid and a necrotic embolus in the central retinal artery. The choroid, optic nerve, and intra-arterial emboli also showed irregular infiltration with polymorphonuclear cells.

The necrosis was most severe in the optic nerve and retina (Fig. 11), including the macula. The nerve head had been extensively invaded by macrophages,



Fig. 10 (Cogan and Wray). Case 2. Posterior ciliary arteries on nasal side of the right eye showing partial occlusion by a hyaline substance with scarcely recognizable myxoid tissue (PAS, ×80).

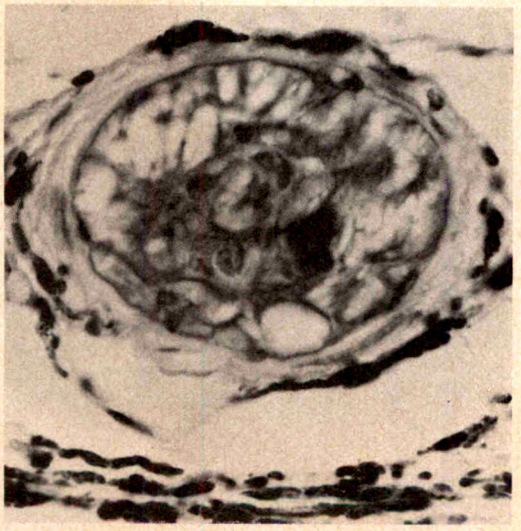


Fig. 9 (Cogan and Wray). Case 2. Myxoma obliterating a choroidal artery (Alcian blue, ×512).

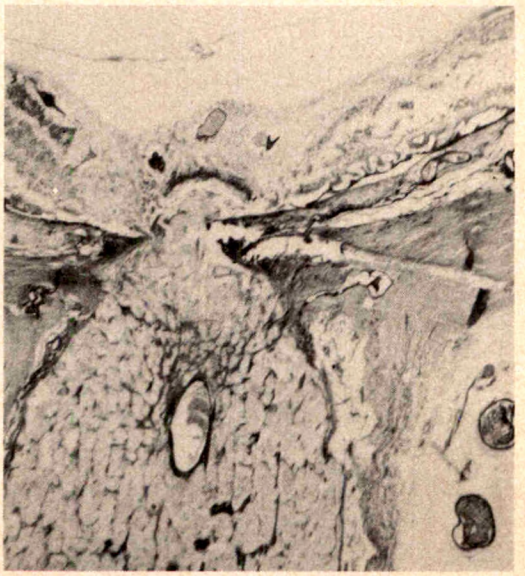


Fig. 11 (Cogan and Wray). Case 2. Papillary region of the left eye showing severe necrosis of the intraocular nerve head and adjacent retina (PAS, ×14).

granulocytes, and by cells whose pyknotic nuclei could not be identified. The layers of the retina could be identified but were vastly loosened and autolysed (Fig. 12).

The myxomatous emboli in the posterior ciliary arteries had the same morphologic appearance as in the right eye (Fig. 13). Some were infiltrated by polymorphonuclear cells. The main choroidal arteries and the central retinal artery on the disk (Fig. 14) were also distended by myxomatous emboli but the peripheral vessels in both the choroid and the retina were patent. The choroid adjacent to the disk was necrotic and contained necrotic intra-arterial emboli (Fig. 15).

One of the ciliary vessels on the nasal side of the optic nerve showed the same transmutation of myxomatous tissue into hyaline substance as had been noted in the corresponding artery of the fellow eye.



Fig. 13 (Cogan and Wray). Case 2. Posterior ciliary arteries of the left eye distended with myxomatous tissue. The smaller vessel in the upper right region has a small lumen containing red blood cells (PAS, ×60).

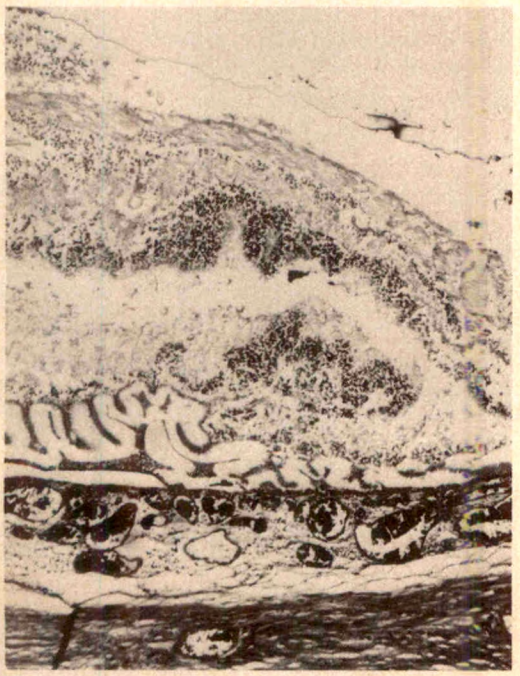


Fig. 12 (Cogan and Wray). Case 2. Cecocentral portion of the retina of the left eye showing extensive necrosis of recent origin (PAS, ×80).



Fig. 14 (Cogan and Wray). Case 2. Magnified view of the central retinal artery of the left eye (seen in Figure 11) showing complete occlusion of the artery by myxomatous tissue and necrosis of the surrounding tissue (PAS, ×184).



Fig. 15 (Cogan and Wray). Case 2. Necrotic choroid in region behind the macula of the left eye containing necrotic vessel with disintegrating substance that is presumably myxomatous tissue (PAS, ×32).

Discussion

These two cases, together with the previous eight, emphasize the importance of considering myxomatous emboli whenever occlusive vascular disease in the eye is associated with unexplained neurologic disease or in persons with suspected subacute bacterial endocarditis who have no prior history of rheumatic fever.

Although most of the previous reports described occlusion of the central retinal artery without visible emboli, our first patient had white material in the retinal arteries that was probably myxomatous tissue. Anderson and Lubow[3] described similar material in a patient as "cream cheese-like material" and also interpreted as myxomatous emboli. Actual emboli were not described clinically in the other cases. Subsequent follow-up (20 months in our case and five months in Anderson and Lubow's case) showed disappearance of the material in the retinal artery. This suggests that the tumor emboli do not grow under the conditions of their transplantation into the vessels within the eye. The opposite conclusion has, however, been drawn in the cases of emboli in cerebral vessels.[8]

Our second case confirms the histopathologic occurrence of myxomatous emboli in the retinal, ciliary, and choroidal arteries. The chorioretinal lesions seen ophthalmoscopically probably represented infarction but, as is well known with occlusive disease of the choroid,[9] the chorioretinal changes were poorly correlatable with the actual site of obstruction in the artery. Our second case was unique in the eventual bilateral involvement of the eyes. The necrotizing papillitis of the left optic nerve found post mortem with involvement of the adjacent choroid and retina is similar to what was described by Manschot[5] as juxtapapillary chorioretinitis and could well be the histopathologic counterpart of the unusual clinical picture described by Campbell.[4] The combination of central retinal artery occlusion, ischemic optic neuropathy, and juxtapapillary choroidal involvement all in one eye, as in these three cases, is sufficiently unusual to warrant particular suspicion of a myxomatous origin. We previously have seen such a rare combination only in temporal arteritis.

Of the ten cases of retinal artery occlusion with myxomatous emboli, nine were associated with recurrent neurologic involvement, usually pointing to disease of the ipsilateral middle cerebral artery. This may be an important clinical clue in differentiating a myxomatous (or other embolic) origin from local vascular disease.

The left eye was apparently involved exclusively in seven of the ten cases (attributed to the more direct takeoff of the left internal carotid artery[2]), the right eye in two, and both eyes (our Case 2) in one. The choroid or juxtapapillary area was noted to be involved clinically in two previous cases[4,5] and in one of our cases.

Although myxomatous emboli have now been demonstrated in the choroidal arteries in only two cases (that of Jampol, Wong, and Albert[2] and ours), all four cases studied histopathologically[2,5,6] (including our own) showed involvement of the ciliary arteries. It is presumably this latter which accounts for the unusual association of ischemic optic neuropathy with the retinal artery occlusion.

Since atrial myxomas are treatable if recognized in time but are otherwise fatal[10] an early correct diagnosis is important. Such a diagnosis should be considered ophthalmogically whenever occlusive disease in the eye occurs in association with repetitive neurologic symptoms suggestive of ischemic origin. The diagnosis is all the more to be suspected when the left eye is involved and when ischemic optic neuropathy or choroidal involvement accompanies the retinal artery occlusion. Appropriate angiographic studies or ultrasonography can be done by cardiologists to establish the diagnosis but the ophthalmologist's role is, as charged by Soma Weiss, to think of the diagnosis in the first place.

Summary

Vascular occlusion in the eyes from cardiac myxomas was diagnosed in two cases, belatedly in one and not until after death in the other. Suspicion of a myxomatous origin should be aroused by the combination of unexplained retinal (or choroidal) vascular disease occurring with multifocal neurological symptoms and with systemic symptoms suggesting atypical subacute bacterial endocarditis.

The first patient had unilateral retinal artery occlusion by embolic material believed to have been myxomatous. Removal of the cardiac myxoma resulted in disappearance of this material (although the eye remained blind).

The second patient who had had evidence of retinal artery occlusion in the clinical course of her multisystemic disease was found at autopsy to have extensive myxomatous involvement of the posterior ciliary arteries and of the choroidal arteries of both eyes and of the retinal artery in one eye.

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30-YEAR OBSERVATION OF PATIENTS WITH EALES'S DISEASE

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It is a great honor to join with my colleagues in paying tribute to the Michael Hogan Festschrift. Michael Hogan is one of the great clinical academicians in ophthalmology. His many patients love and respect him for his kindness, good judgment, and wisdom, while his colleagues deeply appreciate his rapport and advice over many years. He is a Titan among men, a great leader, and a thorough professional. It is always a joy and pleasure to be in his company both in a professional surrounding and in his gracious home.

I first became interested in the poorly understood syndrome of Eales's disease in the latter years of World War II. Young pilots and aircrew members with this condition were in prime physical condition and had been subjected to many medical examinations, especially detailed ophthalmologic examination. The typical serviceman with Eales's disease complained of floating spots before one eye with no appreciable blurring of vision. The Air Force base general medical officer usually recorded normal visual acuity findings and ordered the serviceman back to his aircrew duties. Several aircrew members were labeled as having "Channel Fever" by these medical officers, who suggested that they were complaining to avoid further combat duty over the English Channel. As the complaints persisted, eventually the pilot was referred for an ophthalmologic consultation. I examined approximately 15 such healthy young Air Force personnel during 1944 and 1945.

Henry Eales[1] provided the first report of this disease in the English language. The original descriptions by Eales in his classic report have not been improved on.

Many German ophthalmologic reports followed, but the disease as a possible clinical entity had not been firmly settled. Duke-Elder[2] stated in 1941 that "it is not a disease entity but a clinical manifestation of many diseased conditions."

In 1958, Donders[3] published a magnificent review of Eales's disease and included 100 patients with Eales's disease. I have published[4–6] several reports on periphlebitis retinae (Eales's disease) since 1948.

Since 1969, there have been a few reports, mostly in the German opthalmic literature, but most authors referred either to a few patients treated with photocoagulation or to peculiar abnormalities noted by fluorescein angiography after photocoagulation of the neovascularized lesion.

SUBJECTS AND METHODS

Many pilots were examined at the Veterans Hospital after the war, and a repository of valuable clinical material was gathered in one clinical ophthalmic facility. Standard ophthalmology textbooks at that time indicated that the condition was a poorly understood clinical syndrome and possibly not one clinical entity but a combination of other similiarly poorly understood diseases in which recurrent hemorrhages occurred into the retina or into the vitreous cavity.

In 1948, a young Air Force pilot had recurrent hemorrhages in both retinas. His referring ophthalmologist had diagnosed occlusion of the central retinal vein, which highlights the difficulty at

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times in differentiating between occlusion of the central retinal vein and periphlebitis retinae. The patient developed an acute fulminating pulmonary tuberculosis in the hospital. Two or three months later his condition had deteriorated rapidly and he died. Before his death repeated sputum examinations with guinea pig inoculations revealed a confirmed active tuberculous infection in the lungs. A complete autopsy was performed and many caseous tuberculous glands were found in the mediastinum and peritoneal cavity. Both eyes were obtained for pathologic study and details from the microscopic examination of the eyes have been published.[5] Briefly, they indicated a nonspecific allergic type of reaction around the walls of the peripheral veins in the retinas with no signs of the tubercle bacillus or granulomata. Earlier authors have suggested the possibility of active tuberculous infection in the eyes in periphlebitis retinae.

About 1950, two young, healthy aircrew personnel were admitted to the Veterans Hospital, with the classic findings of periphlebitis retinae with intraretinal and vitreous hemorrhages. For about three months both received massive antituberculous chemotherapy with para-aminosalicylic acid and streptomycin, fairly standard therapy at the time. Maximum chemotherapy medication was continued until deafness occurred. During this period both patients, while receiving massive antituberculous chemotherapy medication, developed larger vitreous hemorrhages. This observation refuted the current presumption that the condition was due to an active tubercle bacillus and lent weight to the developing view that the etiology was not active tuberculosis.

I noted that most of these patients had consumed unpasteurized milk in their childhood. Most of the patients grew up in a rural or farm setting rather than in an urban area. A few patients had had a history of a healed active pulmonary infection but most had a positive skin tuberculin test. Many had enlarged mediastinal lymph glands without signs of active pulmonary tuberculosis.

I complied these basic clinical observations during the first ten years from approximately 30 patients with periphlebitis retinae.

About two thirds of the patients were young men approximately 20 years old, and one third were women who were appreciably older. The presenting symptoms were transient, unilateral, mild blurring of vision in most patients, with occasional severe blurring of vision from a vitreous hemorrhage. The severe hemorrhagic blurring often cleared within one or two weeks from the absorption of the vitreous hemorrhage or the gradual settling of the hemorrhage inferiorly. I noted exceptions in several patients who had almost complete loss of vision and an essentially black ophthalmoscopic reflex present for six to nine months. In most of these patients the vitreous hemorrhage gradually absorbed nine months later. There was return of essentially normal visual acuity from a functional point of view.

The natural course of the disease was three to five years. However, some patients had acute periphlebitis retinae with the classic findings of Eales's disease that completely resolved within six months; the ophthalmoscopic findings were essentially normal. Conversely, several patients were observed who had disease states prolonged for more than 40 years. One man, now 70 years old, had his first massive vitreous hemorrhage at 19 years of age. Two years ago he had a severe vitreous hemorrhage in one eye with marked loss of vision that gradually absorbed. Visual acuity is normal.

Although most patients under observation during the past 30 years have had obscured vision for days to months, there

were few who had permanent loss of vision in one or both eyes. Only one of 135 patients with Eales's disease had bilateral permanent loss of vision, necessitating the patient to be registered with the Institute for the Blind. Thus, patients with Eales's disease rarely suffer appreciable, permanent loss of vision.

Discussion

Eales's disease should be considered a clinical entity and not a manifestation of many disease conditions. There is probably a transient phase not commonly seen in which the veins show an inflammatory reaction in the associated perivenous exudation and possibly some vitreous cellular activity. Typically, in the acute stage there are hemorrhages from the peripheral retinal veins, perivascular sheathing along the walls of the veins, and, in many instances, hemorrhages into the vitreous cavity. In an earlier study,[5] the hemorrhages and exudation resulted from a delayed local hypersensitivity in the walls of the peripheral retinal veins in individuals sensitized to the tuberculoprotein antigen. Histopathologic evidence presented in previous reports[4–6] supported this hypothesis.

Initially, the patient has sudden blurring of vision because of a vitreous hemorrhage. If the hemorrhage is not severe, the site of the extravasation is observed ophthalmoscopically from a retinal vein in the midretina or in the retinal periphery. Frequently, small peripheral varicosities in the veins were noted in the fellow asymptomatic eye.

Retinal pathologic findings are generally confined to a periphlebitis involving one or more of the retinal veins and rarely occur in the arteriolar vessels in the midretina. Classically, the retinal pathologic findings were confined to the midretina and peripheral retina, although occasional perimacular hemorrhages have been observed. In several patients there were ischemic changes in large segments of the retinal periphery in periphlebitis retinae. Frequently there is an arcade of connecting venules peripheral to the anoxic retina.

Although the presenting finding is usually a sudden marked blurring of vision in one eye from a large vitreous hemorrhage, a routine ocular examination may show evidence of long-standing retinal pathology with extensive perivenous sheathing and retinitis proliferans. The patient is relatively asymptomatic because the vitreous hemorrhages or intraretinal hemorrhages are minimal.

History—Patients with suspected periphlebitis retinae must be questioned as to the history of tuberculosis or pleurisy or contacts with patients with tuberculosis; whether or not the patient consumed unpasteurized milk as a child; and the geographic location of childhood years. Patients with this disease who were raised on a farm and who consumed unpasteurized milk were often Canadian born. There were relatively few urban Canadian-born patients in this series. The disease never occurred in family members and there was no evidence of a hereditary tendency.

The complete medical examination should include blood studies for sickle cell disease, serum electrophoresis, thalassemia, complete blood cell count with differential, bleeding and clotting times, platelet count, chest x-ray examination, and intradermal skin tuberculin test.

In several patients, the lesion started in the classic manner with extensive midretinal or peripheral venous hemorrhages; suddenly, an acute posterior or an anterior uveitis developed in one and often both eyes. With the onset of the severe uveitis the retinal hemorrhages became more marked and extensive throughout large areas of the retinas. These patients often had concomitant edema around the maculae so that there was usually an

appreciable loss of central vision. The active periphlebitis with retinal hemorrhages appears to precede the severe posterior uveitis but in some patients the severe posterior uveitis was present when the patient was initially examined. Infrequently, patients had an associated pars planitis with an outpouring of leukocytes into the anterior vitreous cavity.

Physical exercise or physical stress has not been a factor at the time of the precipitating vitreous hemorrhage. Vitreous hemorrhages frequently have occurred during sleep and are apparent to the patient on awakening. Vitreous hemorrhages are usually induced by vitreous contraction at the site of a blood vessel. The decreased vascular blood pressure and sluggish venous circulation may cause the vitreous hemorrhage in an already diseased blood vessel wall.

I diagnosed sickle cell disease in one patient, a young black Canadian-born woman.

Not all patients with Eales's disease have recurrent vitreous hemorrhages. Many patients had chronic periphlebitis with sheathing but no neovascularization and vitreous hemorrhages developed later.

In the age-sex distribution, the youngest girl was 16 years of age, had consumed unpasteurized milk, and had sudden bilateral vitreous hemorrhage. The youngest boy was 11 years of age when he had a massive vitreous hemorrhage in one eye with visual acuity of light perception; four years later visual acuity in the eye was essentially normal.

There is no apparent relationship between the activity of the disease and the use of contraceptive medication in young adult women.

Branch venous occlusion—This is the most common condition confused with periphlebitis retinae. Occasionally, a complete occlusion of the central retinal vein is mistaken for periphlebitis retinae. However, patients with venous occlusions are usually in the fifth to sixth decade and usually there is macular pathology with fairly marked permanent loss of central vision in the affected eye. In the later stages of retinal venous occlusion, newly formed veins occur close to the optic disk. These veins are large, while in periphlebitis retinae the neovascularized lesions are most frequently in the mid- or peripheral retina and are relatively small.

The retinal findings in diabetes, polycythemia, periarteritis nodosa, and macroglobulinemia occasionally may simulate this condition.

Acute massive vitreous hemorrhage—I admit patients with this condition to the hospital for complete bed rest to allow the vitreous hemorrhage to settle inferiorly in the eye. After eliminating the possibility of active pulmonary tuberculosis, these patients receive massive systemic corticosteroid therapy and subconjunctival corticosteroid injections, two to three times weekly, in the affected eye. Some feel corticosteroid therapy is not indicated at this point as the inflammatory stage has passed. I use this regimen in patients with severe posterior uveitis or pars planitis associated with periphlebitis retinae. Immunosuppressive agents have not been advocated.

Chronic periphlebitis retinae—I have used many forms of therapy for chronic periphlebitis retinae including desensitization with tuberculin, roentgen ray treatment, chemotherapy, diathermy, and subconjunctivally injected corticosteroid. These forms of therapy have been replaced by photocoagulation of the neovascularized lesion.

During the past ten or 15 years, I have used repeated light coagulation of the neovascularized areas either with the xenon photocoagulator or with argon laser. Although light coagulation will not always prevent more vitreous hemor-

rhages, this mechanistic form of therapy has markedly reduced the frequency of vitreous hemorrhages. The use of photocoagulation is not without its problems, especially if the lesion is photocoagulated near the macula. Photocoagulation of a vitreous frond is also somewhat hazardous as there is a risk from further massive hemorrhage during the photocoagulation. However, this is a calculated risk and the base of the frond should be photocoagulated if at all possible. It does not seem wise to attempt to photocoagulate lesions near the optic disk margins.

Fluorescein angiography—The use of fluorescein angiography is routine in patients with periphlebitis retinae. The findings have not been contributory and the added knowledge has been limited. Nonetheless some peculiar vascular anomalies, for example, choroidal and retinal anastomoses, have occurred after light coagulation. In addition, fluorescein angiography has revealed arteriolar leaks. It also may reveal small aneurysms which leak dye and these benefit by photocoagulation. In the acute stage there is leakage from the large veins near the disk.

Summary

Of 135 patients with Eales's disease, two thirds of the patients were men around 20 years of age at the onset, while the women were older. The disease continued from six months to 51 years. Several patients were followed for 40 years. The prognosis for useful vision was good as only one patient became blind in both eyes.

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AN ANALYSIS OF SOME CONCEPTS CONCERNING CHRONIC SIMPLE GLAUCOMA

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Whereas clinical research work in glaucoma was often touched with speculation and fantasy 50 years ago, today we are disposed to look pragmatically at the problem. While mathematicians rack their brains over the foundations of probability calculus and statistics, clinical research workers often simply accept the results of statistical manipulations without further analysis and praise them as being the height of objectivity. Yet questions such as the following force themselves upon the mind: (1) How far is it justified to make a sharp distinction between ocular hypertension and beginning simple glaucoma? (2) Given two so-called glaucoma tests, one with 10% false-positive and 12% false-negative results, the other with 20% false-positive and 15% false-negative results, is the first really better than the second? Analysis of the first problem only will be my concern in this paper.

Glaucoma is the disease in which the intraocular pressure is too high for continued maintenance of visual function. The ultimate diagnostic aim in chronic glaucoma must be to determine the upper limit of nondamaging intraocular pressure—the critical pressure—in every case. We are still far from this goal. However, there is an approach to it which is not so satisfactory but interesting by its implications.

The probability of a damaging intraocular pressure is high for a pressure of 32 mm Hg, low for a pressure of 20 mm Hg, but theoretically a probability of damage exists also for a pressure of 14 mm Hg. It is extremely small but is mathematically expressed as a positive figure. We have a distribution of frequency of intraocular pressure—Statistics 1. If we say that 2% of the population has an intraocular pressure of between 21 and 25 mm Hg by applanation, it means that if we choose any one individual of the population, then the probability of finding that he has an ocular pressure of between 21 and 25 mm Hg is 1/50. Finding his pressure to have this value does not suggest that the probability of damage is 49/50.

Other statistics should refer to the relationship between the intraocular pressure and probability of damage to the visual system (Statistics 2). The higher the intraocular pressure the higher the probability of damage. This we know, but we do not know the characterizing figures as we do for Statistics 1. Only experience has taught us that the mean intraocular pressures of 25 mm Hg and higher by applanation are generally not tolerated without damage to the visual field for an indefinite time. But we do not know if the probability of damage in the course of time is .8, .9 or .95 for a pressure of 25 mm Hg by applanation.

Our knowledge of the distribution of frequency of the intraocular pressure being great and our knowledge of the distribution of damage with pressure being slight, other statistical relationships are almost unknown. For example, what is the average increase of a given intraocular pressure in a given time (Statistics 3)? A certain correlation between this increase and the actual increase of pressure has not been defined.[1-3] Such a correlation must be slight. This finding has great theoretical and practical importance. For

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practical purposes there exist cases with pressures around 25 mm Hg by applanation that spontaneously exhibit lower mean pressures some years later. Was former treatment involved? Will pressure increase again later?

Finally, still other statistics (4) would also be important: the statistics of the probable time from the onset of a given pressure until the appearance of a defined visual field damage. We only know that in cases with pressure values common in simple glaucomas, approximately one to two decades pass on an average before easily detectable scotomas are found.[4]

Only because high intraocular pressures have a greater probability of causing visual damage (Statistics 2) than lower ones and because higher values are rarer than lower values (Statistics 1) there is a correlation between rare (high) pressures of Statistics 1 and frequency of damage (Statistics 2). Therefore, the opinion is unfounded that low "normative" also means low critical pressure. In a case with high intraocular pressure but without visual field defect, exists a great (exact data unknown) probability that this pressure is above the damaging limit for this person (his critical pressure), that is, that it will in time (in which time? Statistics 4) cause a visual field defect. Therefore, only the diagnosis "suspicion of beginning glaucoma" is justified. The diagnosis "ocular hypertension" as of a state essentially different from beginning glaucoma would be justified only under two conditions: (1) If we know that the present high pressure is below the critical pressure of the eye. But at the present moment we have no method by which to determine this. (2) If the patient dies many years later without having developed any visual field defect. Even then some doubts remain because of our poor knowledge of Statistics 4. From what we have hitherto said, two procedures are possible when we suspect a beginning glaucoma because of increased pressure without any visual field defect.

1. We believe that the probability of damage is high enough in time to justify treatment by means of drugs.

2. We wait and observe without treatment until the first signs of damage (that is, a scotoma) appear.

There is not much to be said about the first point of view. We ourselves endorse it and generally fix the pressure for introducing therapy by eyedrops at 25 mm Hg by applanation. (We keep patients with pressure values between 22 and 25 mm Hg applanation under observation.) "Generally" means that there may be cogent reasons influencing the ophthalmologist not to adhere to a rigid rule (patient's age, unsatisfactory effect of treatment, working conditions, psychical condition of the patient). But I wish to insist again that 25 mm Hg is an arbitrary value born of my experience as an ophthalmologist. If someone else insists on taking 27 mm Hg as his lower limit for action, nothing can be said against it, except personal experience and feeling. Correctly it should be stated: As soon as the probability of damage due to a pressure value is, let us say, 85% we should begin treatment even without visual field defect. But it is still unknown if this probability is reached at 24, 26, or 28 mm Hg applanation, and even 85% would have to be fixed by agreement.

The second procedure of the ophthalmologist, waiting for scotoma, is legalistic in principle. As long as a defendant has not been judged it is illegal to call him a criminal. Defendant or suspect is equated with ocular hypertension; criminal with beginning glaucoma, that is, high pressure and visual field damage; judged or convicted is equated with appearance of scotoma. Such a juridical point of view, which is not a scientific one but accepted

at present by many ophthalmologists, does not solve the problem; it only shifts it. If the scotoma has appeared, treatment by drugs is begun. But now the question arises as to how far the pressure must be lowered to become ocular hypertension or normal, that is, what is the pressure that satisfies the ophthalmologist's demand for sufficient probability not to be damaging. We have now reached the point where the supporters of the first procedure were from the beginning. What is gained is a kind of "closed season" that is more or less trying for the patient because he has to remain under observation, and observed by a method which, to be candid, as carried out by many is still not satisfactory, perimetry. But the problem of perimetry is the same for ophthalmologists who do not postpone treatment until scotomas appear.

I called waiting for scotomas a legalistic, not a scientific, procedure. It is possible to disagree and to say waiting for scotoma is a scientific experiment. The experience of the research worker, the ophthalmologist, will be increased when the scotoma appears. Now he knows that the present pressure is too high. Put this way, it immediately becomes clear that the experiment is scientifically correct but as a form of medical behavior it seems open to doubt. Clearly a time-honored principle has been violated, primum non nocere. Where there is a great probability of doing more harm than good to a patient by any procedure this procedure must be avoided, even if it is a good scientific experiment.

In cases of probably damaging pressure (without scotoma), there is no doubt that we diminish the danger of a later damage in such a case by lowering pressure by means of medication. But what if we do not succeed at all or succeed only insufficiently? Do we do more harm or more good to such a patient if we now proceed to an operation or if we continue to wait with the best available medical treatment until a scotoma appears? Taking into consideration that every operation has some risks, that almost every antiglaucomatous intervention is followed by a decrease of visual acuity, at least a transitory one, that many of these interventions accelerate the development of cataract, everyone will understand what we believe is the correct course in these cases: to wait for a small scotoma before proceeding to an operation.

As can be seen, in principle we are in favor of the first procedure but we have often violated this principle because there are many uncertainties which the distinction between ocular hypertension and suspicion of beginning simple glaucoma does not remove. What really exists are pressures with greater or lesser probability of damage. The unsatisfactory state of affairs will diminish but not disappear if we know the actual values of the probabilities. Our ignorance cries out for knowledge of the critical pressure in every case either with or without scotoma, in cases with high or with low intraocular pressure. No so-called provocative test provides us with this knowledge.

To return to Statistics 3, we only know that, until now, results have been unexpected. Unexpected because we believe that obstruction of the trabecular meshwork (or sometimes restriction of the outflow channels of Schlemm's canal) is the basis of increased resistance in simple glaucoma. That is a pathologic mechanism that makes us expect a gradual increase of resistance in the course of time. Undoubtedly there exist "secondary glaucomas" caused by obstruction of the trabecular meshwork. However, the findings of Holmberg[5] and of Tripathi[6] showed that the passage of aqueous humor through the endothelium of Schlemm's canal is chiefly transcellular

and not intercellular. The possibility suggests itself that certain glaucomas are caused by some change in this mechanism. It seems understandable that changes of this kind may proceed both in the direction of increased resistance and also in the direction of decreased resistance from any given level of pressure. This would give just the results shown in Statistics 3. The practical conclusion for us in cases with pressure around 25 mm Hg applanation is to discontinue any medical treatment from time to time for some days to determine how the pressure responds in the untreated eye.

In 1955 Gafner and Goldmann[7] published a theory and its electrical model explaining why increased pressure would damage primarily the region of the optic disk, as found in glaucoma, because there are special conditions of the local circulation (shunts). By fluoroangiophotography, Hayreh[8] showed that such conditions probably exist. Therefore, we have reasons for admitting that the intraocular pressure damages the papillary tissue influencing the circulation of the blood in the papilla. Accordingly we may now change our definition of glaucoma. It is the disease in which the intraocular pressure is too high for a sufficient circulation of the blood to be maintained in the papilla for the continued survival of its tissue. This definition implies that every drug that changes the circulation in the papilla independently of its influence on the aqueous dynamics also changes Statistics 2. Every pressure value will now have a probability of damage different from that before the use of the drug. Such constellations do exist. Heilmann[9] has shown that clonidine diminishes the intraocular pressure but at the same time also the general blood pressure. Therefore, relative scotomas in a case of simple glaucoma diminish if the intraocular pressure is lowered by acetazolamide (Diamox) but do not diminish if the pressure is lowered to the same degree by clonidine. Adrenalin 1 to 2% drops can damage the macular region not only in aphakic eyes[10] but also in phakic eyes,[11] apparently by disturbing the circulation of this region. These drugs may also influence the disk circulation, decreasing the critical pressure of the treated eye. We do not know it and we shall not know enough about it as long as we are unable to determine quantitatively the circulation of the blood in the disk in every single case or to determine the individual critical pressure. Statistics and probabilities are not sufficient.

SUMMARY

Glaucoma is the disease in which the intraocular pressure is too high for continued maintenance of visual function. The upper limit of nondamaging pressure must be determined in each case. Our actual knowledge is restricted to some incomplete statistics correlating intraocular pressure to its probability to be damaging to the optic nerve. Despite their scarcity these correlations allow us to draw conclusions of some theoretical and practical interest.

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THE ART OF PERIMETRY

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There is an art to the proper examination of the visual field which is being more and more neglected in recent years. There are a number of factors responsible for this neglect.

With the increased complexity and sophistication of the instruments of perimetry there is a tendency to view the visual field examination as a wholly scientific procedure, the end result of which is an objective measurement of visual function that is immutable, exact, and repeatable. The fallacy of this view is readily seen when one realizes that visual field examination, perhaps more than any other ophthalmologic test, is a psychophysical evaluation of an individual's visual and mental status, at a given time. No matter how elaborate the instruments and techniques used the test is subjective, cannot be considered truly scientific, and in many ways is more an art than a science.

The only truly scientific method of visual field examination is the objective measurement of visual evoked response of the optic cortex. Variations of this technique have received increasing attention in the last ten years.

Recently Cappin and Nissim[1] succeeded, despite great technical difficulties, in objective detection of early visual field defects in glaucoma. They plan further work, using phase-sensitive detectors to investigate the possibility of visual evoked response changes anticipating subjective visual field defects and clinically evident optic nerve damage in patients with increased intraocular pressure.

The more complex the instrumentation becomes the more time must be allotted for the examination. With more demand on the ophthalmologist's time to include an increasing number of complicated procedures in a routine eye examination, less time is allowed for visual field testing. Faced with the need to do tonometric, tonographic, gonioscopic, fluorescein angiographic, ophthalmoscopic, photographic and microscopic, and slit-lamp examinations—all objective tests—the harassed clinician understandably delegates such subjective examinations as history taking, vision testing, refraction, and perimetry to paramedical personnel.

These subjective examinations, in many respects the most important in the patient's mind, require a degree of psychic evaluation that will often determine the validity of the findings.

There must be good rapport between examiner and patient. Patient responses to stimuli must be evaluated during the examination itself. This is especially true of visual field testing. The visual field examination cannot be isolated from the total evaluation of the patient. Even the best technician, with inexhaustible patience, cannot convey to the clinician how responsible a given patient's answers are. The physician must assess these values himself. The more important the visual field studies are to the establishment of a diagnosis the greater the need for flexibility in the examination and for the personal attention of the clinician responsible for the diagnosis. Almost all ophthalmologists will admit this and most will agree that perimetry is one of the most valuable of all examination techniques available to them. Few realize, however, that perimetry is not an exact science and that only the physician himself can practice the art of perimetry.

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A well-trained technician is a necessity to the clinician who believes that he simply does not have the time to examine visual fields. But such a person must be trained in more than the mechanical recording of the appearance of stimuli in the various areas of the field.

In view of the widespread anatomic distribution of the visual system and the fact that large and small lesions in this system can affect the visual fields, a perimetric technician must have a thorough knowledge of the anatomy of the system, what types of lesion are most likely to affect specific areas, and whether the patient's subjective responses to stimuli can be trusted. This assumes a great deal of responsibility on the part of a lay person, and most are unwilling to undertake it.

If, however, the physician is willing to oversee such examinations so he can be the judge of their validity, he can utilize the technician as a "screening device," study and analyze the field defects himself, and when necessary, examine more precisely the deficient area.

It is unfair to a lay technician to present her with a Goldmann perimeter, teach her how to use it to record a kinetic visual field examination, and expect her to analyze accurately all existing field deficits with this one instrument. Unfortunately this is only too often what is done. Neither can one detect all the possible defects in a given patient with a 1-meter tangent screen. Nor will static perimetry, no matter how well done, provide all the answers to the problem of defect detection.

Flexibility is the key to accurate diagnostic perimetry. The examiner must suspect the existence of a defect in the visual field and must choose the perimetric technique most suitable for its detection and analysis. This is the aim[2] and the art of perimetry.

A few case reports should serve to illustrate these points.

Case reports

Case 1—A 65-year-old patient suspected of having glaucoma was referred with moderately elevated intraocular pressure and large deep optic cups. There was no visual field defect when examined kinetically on a Goldmann perimeter. A study of the 1/2000 isopter on the tangent screen showed a questionable deficit in the form of a vague relative scotoma just above and nasal to fixation. When this area was studied on the Tübinger perimeter of Harms and Aulhorn by the static method of perimetry, using light threshold sensitivity to plot the profile of this specific area of suspected field loss, it became evident that there was a definite early nerve fiber bundle defect close to fixation and extending nasally to a small horizontal step. Static perimetry revealed the existence of nerve fiber damage, but only after such damage had been suspected and only by the use of the most exquisite sensitivity tests. Such careful, time-consuming, quantitative perimetry was necessary to establish a diagnosis of glaucoma and a baseline for future examinations. Even though the actual examinations (except for the tangent screen test) were done by a lay technician they were guided by the close supervision of the clinician.

Case 2—A 60-year-old man was brought by his wife for examination because she had noted that he seemed to have increasing difficulty in reading and a tendency to drive his car directly over the white line on the highway. She had also noted progressive memory loss and what she described as "confusion."

The patient denied all symptoms, but in answering questions occasionally chose an inappropriate word. Visual acuity by Snellen letters was 20/20 in each eye at both near and distance, but considerable difficulty was encountered in reading words even in large print. He had no trouble in spelling out the letters in a word. Except for some retinal arteriolar narrowing the objective examination of the eyes including tonometry was normal.

Attempts to examine the visual fields were frustrating and variable with both large and small stimuli on tangent screen or perimeter. No two tests along a given meridian gave the same result. At times the upper field was depressed and at others the lower field was lost. Most of the meridia, however, appeared normal even in the 2/2000 isopter, when the patient could be persuaded to maintain good central fixation.

When, however, the patient was confronted with two simultaneously exposed stimuli, one on each side of the tangent screen, he consistently failed to see the one in the right lower field of each eye. When the target was removed from the left visual field he again saw the stimulus on the right. This "extinction" of the stimulus in the right lower field could be demonstrated monocularly or binocularly and with double stimuli varying from 2 to 20 mm and even by confrontation testing with two moving fingers. It would not, of course, have been possible to demonstrate this important field loss by even the most careful and expert routine perimetry.

This single subjective sensory loss is almost pathognomonic of a lesion of the left parietal lobe; in this case a vascular accident with cerebral cortical infarct.

Case 3—A 58-year-old man was referred for low-tension glaucoma because of the finding of a broad dense arcuate scotoma in the left eye with peripheral "breakthrough" into the nasal field. The right eye had been injured years before and was said to be "blind," with a mature cataract. The left optic disk was moderately cupped and appeared somewhat pale. The intraocular pressure measured 10 mm Hg in the left eye; 8 mm Hg in the right eye. The left visual field, examined by a competent technician on the Goldmann perimeter, showed a dense nerve fiber bundle field defect extending from the blind spot above fixation and breaking through into the nasal periphery both above and below the horizontal. The right visual field had not been examined because of its alleged blindness.

When the left visual field was examined on the tangent screen in the 10/1000 isopter the findings were essentially the same as the Goldmann field except that the inferior nasal breakthrough ended sharply at the vertical border of the lower field defect. The entire lower nasal quadrant was "blind" to all stimuli up to 100 mm. The right eye was now tested with large stimuli and found to have an absolute deficit in the lower temporal quadrant while the other three quadrants revealed only a relative loss for the same test object. Ophthalmodynamometry on the left eye revealed an abnormally low diastolic pressure. The left carotid pulse was absent but no bruit was heard. Left carotid and ophthalmic artery occlusion was postulated with ipsilateral Bjerrum scotoma and contralateral homonymous inferior quadrantanopia. Carotid angiography revealed almost complete occlusion of the left internal carotid artery, which was eventually relieved by endarterectomy. The visual field loss remained unchanged.

Discussion

None of these visual field defects could have been correctly analyzed by the usual routine perimetric techniques. Nor could a correct diagnosis have been made without the application of these flexible, quantitative perimetric studies.

Numerous similar cases could be cited. In many of them the visual field defects were the only diagnostic finding and were missed or misinterpreted because of the limits imposed by a rigid examination technique. In many instances the art of perimetry prevailed over the science.

Summary

There is no single method of perimetric examination which is applicable to all types of visual field defects. Perimetry is a subjective psychophysical sensory examination. It is not an exact science unless one includes the objective measurement of visual evoked response in the optic cortex. Until such a method becomes clinically available it will be necessary for the perimetrist to determine which techniques to use in a given case and to apply these techniques with sympathetic understanding. This is the art of perimetry.

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CHANGE IN CELL TYPE OF HUMAN CHOROIDAL MALIGNANT MELANOMA IN TISSUE CULTURE

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Epithelioid cell malignant melanomas of the human uvea are roughly two to three times more malignant than the spindle cell varieties as judged by difference in mortality of the two groups. Although it had been previously postulated that these two biologically different tumors arise from different stem cells, it is now generally thought that they have the same cell of origin but behave differently because of the direction of their differentiation.

This report concerns the tissue culture characteristics of five choroidal malignant melanomas that spontaneously transformed from spindle cell to epitheliod type and vice versa. The mitotic index of the epithelioid growth was several times that of spindle cell tumor and the generation time was considerably less. Subcultures showed mixtures of the two types with intermediate and mixed forms suggesting a transition from one to the other.

MATERIALS AND METHODS

Cell cultures—The tumors were set up in tissue culture within six hours of enucleation. The uveal tumor was localized by transillumination and a portion of it was included in the calotte. The remainder of the globe was fixed for histologic processing.

Bits of tissue were cut from the center of the tumor, care being taken to avoid inclusion of retinal pigment epithelium or normal choroid, and were placed in a quartered petri dish containing growth media (Eagle's MEM in Gey's balanced salt solution fortified with 15% fetal calf serum and 6 g of glucose per liter). After further mincing, tumor fragments were transferred to a modified Rose chamber[1] containing media and incubated at 36°C. Eight to ten such initial cultures were done in each case. Initially the medium was changed weekly but as the cells proliferated, biweekly exchanges were done.

After the cultures were well established in Rose chambers one such chamber from each case was fixed and stained by May-Grunwald Giemsa for study of cell morphology. When the remaining Rose chambers were saturated by cultured tumor, the cells were removed with 0.25% trypsin and were subcultured in either Rose chambers or in a T-flask.

Monitoring of cell growth—Cultures were observed by phase microscopy. Cell morphology, growth patterns, motility, and generation time were monitored by time lapse cinemicrography and phase photomicrography.

The mitotic index of the uveal melanoma cell cultures was determined by fixing and staining the cultures with Giemsa stain and counting the number of cells per 1,000 that were undergoing mitosis. We used an ocular grid with phase contrast optics at ×400.

Chromosome counts were done by the method of Hungerford.[2] One hundred chromosome spreads were counted in each instance.

Cell generation time denotes the interval between consecutive divisions of a cell. This was done by time lapse cinemicrography over a period of 48 hours.

Cell clone—A cell clone was developed from one (Case 4). A monolayer of cells

From the Estelle Doheny Eye Foundation, Los Angeles, California. This study was supported by Public Health research grant NB-04501-03 through NB-04501-06, the National Institute of Neurological Disease and Blindness, and National Eye Institute grants EY00010-07 and EY00010-08.

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was trypsinized from a T-flask by using 0.25% trypsin. The cells were centrifuged, the supernatent aspirated, and the cells were resuspended in 10 cm^3 of tissue culture medium. The cell suspension was pipetted until there was a uniform dispersion of cells. A cell count was done and the cells were further diluted in tenfold dilutions until the cell suspension was approximately 1×10^2 viable cells per milliliter. Five milliliters of this suspension was further diluted in 45 ml of growth media. This constituted an additional tenfold dilution and yielded a suspension containing approximately ten viable cells per milliliter. One milliliter of this suspension was added to 4 ml of growth medium in a Falcon T-flask. After 24 hours the flask was examined microscopically and the isolated cells were marked with wax pencil. Any cell clumps were removed with a sterile Dacron swab. The flask was then incubated undisturbed for 14 days. At this time, the medium was aspirated from the flask. By use of a hot knife an opening was made above the previously marked area and the small colony of cells known to evolve from a single cell was removed with a sterile Dacron swab and resuspended in 2 ml of tissue culture medium. This suspension was placed in a Falcon flask with 3 ml of

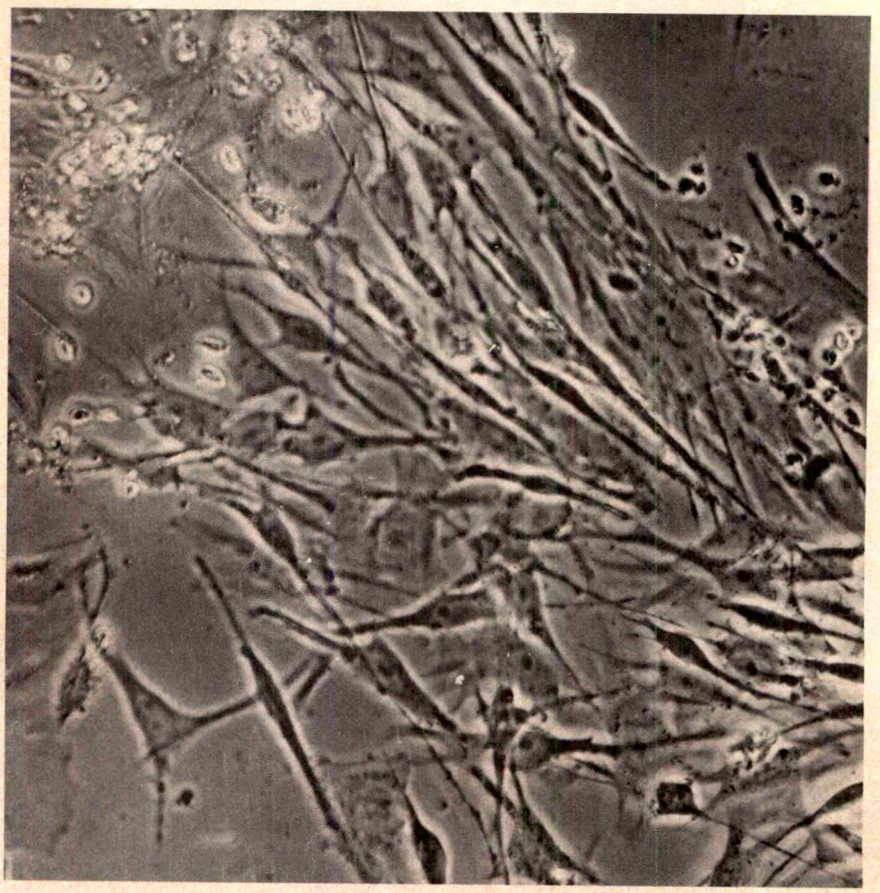


Fig. 1 (Irvine, Mannagh, and Arya). Case 1. Spindle-cell outgrowth in primary culture (phase optics ×200).



Fig. 2 (Irvine, Mannagh, and Arya). Case 1. Mixed cell growth of opithelioid and spindle-cell growth (phase optics ×200).

tissue culture medium and then incubated. This is the only cloning method with which we have had success.

RESULTS

Case 1 was that of a 71-year-old white woman with a spindle-B malignant melanoma of the choroid, measuring 12 × 10 mm. It was set up in tissue culture on Nov. 11, 1965, and cells in the primary culture were spindle (Fig. 1). Epithelioid growth was noted on Dec. 7, 1965, in this culture (Fig. 2). This tumor grew rapidly and remained epithelioid through two transfers. On the third transfer, it became mixed in cell type and subsequently reverted to epithelioid growth (Fig. 3). The mitotic index was 6.5% in epithelioid culture. These cells were transferred 18 times and lost to yeast infection after 18 months.

Case 2 was that of a 45-year-old white woman with a mixed-cell malignant melanoma of the choroid measuring 8 × 4 mm. One Rose chamber containing the primary culture grew out as a spindle-cell tumor, and remained the same through two subcultures lasting three months. A second Rose chamber, of the primary culture, however, grew out initially as a spindle-cell tumor but became epithelioid in the second subculture and epithelioid through four subsequent transfers. It became contaminated with yeast after

four months. The mitotic index was 6.9% on the second epithelioid transfer.

Case 3 was that of a 40-year-old white woman with an epithelioid malignant melanoma of the choroid measuring 8 × 8 mm. Two primary cultures were set up. One of these grew out as spindle cells and remained so through five transfers. The second primary culture, however, grew out spindle cells. The first and second subcultures were composed of epithelioid cells. The third subculture was of pure epithelioid cells. This tumor maintained its epithelioid characteristics through ten subcultures. The mitotic index was 3.6% on the third epithelioid transfer.

Case 4 was that of a 44-year-old white man with a mixed-cell malignant melanoma of the choroid measuring 12 × 10 mm. This tumor was set up on Sept. 1, 1967, and by Sept. 5, 1967, grew out spindle cells (Fig. 4). Six days later epithelioid cells began to appear. Subcultures three through 16 were pure epithelioid growth but subculture 17 showed some spindle cells (Fig. 5). All subsequent transfers

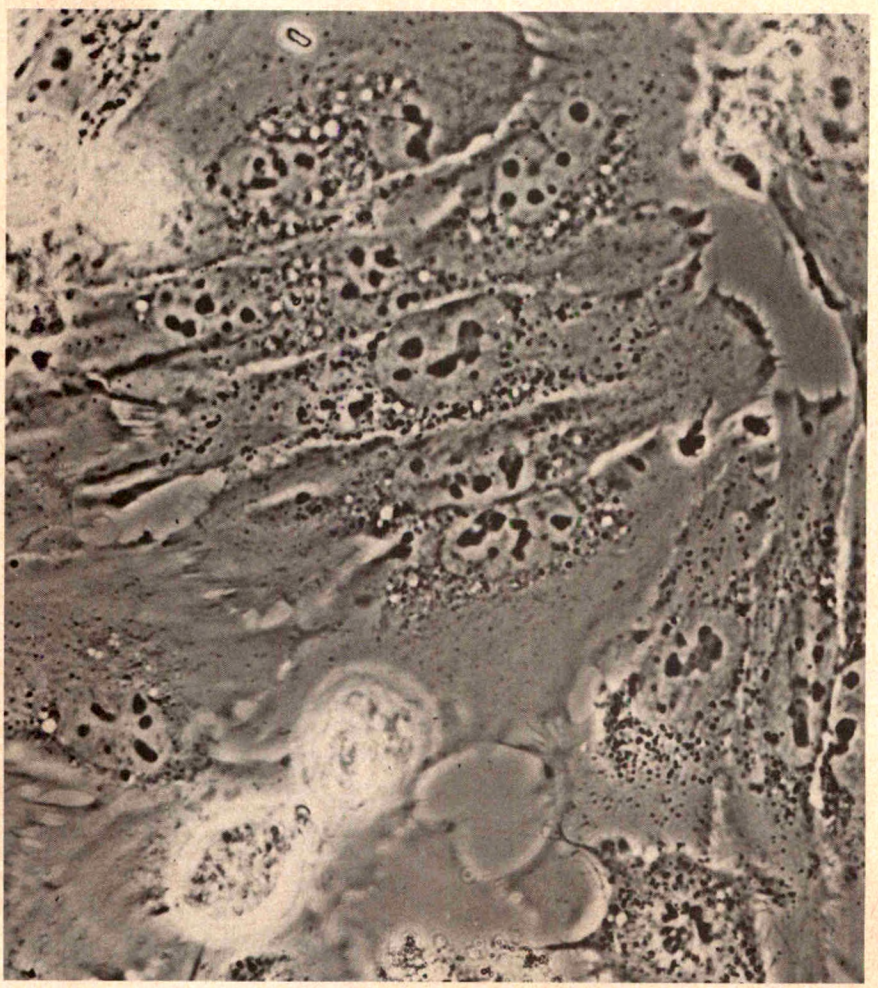


Fig. 3 (Irvine, Mannagh, and Arya). Case 1. Epithelioid cell growth in 12th passage (phase optics ×400).

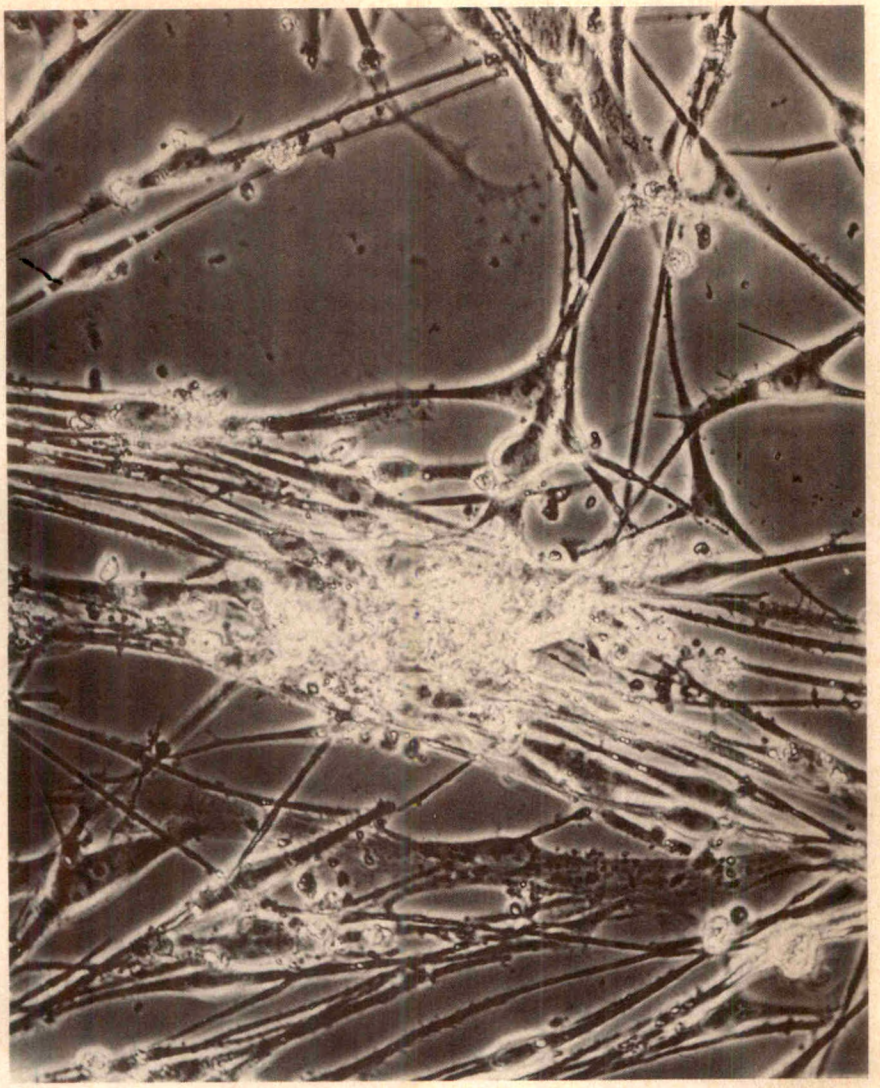


Fig. 4 (Irvine, Mannagh, and Arya). Case 4. Spindle-cell growth in primary culture (phase optics ×200).

were epithelioid and we felt that this tumor spontaneously developed into a cell line (Fig. 6). Intermittently it was frozen and stored. The mitotic index was 7.2%. Chromosome count was 58 to 137. The chromosome modal was 68 = 3n − 1 or hypotriploid. Generation time was 23 and 22 hours. This was compared to a primary 6-day-old culture with a generation time of 29 hours and mitotic index of 1.6%. This tumor has been successfully cloned (Fig. 7).

Case 5 was that of a 54-year-old white woman with a mixed tumor of the choroid measuring 15 × 5 mm. It was set up Sept. 21, 1968, and grew out spindle cells at the first transfer on Oct. 10, 1968. The second transfer grew out epithelioid cells by Dec. 2, 1968. This tumor remained epithelioid through 42 transfers and was lost with

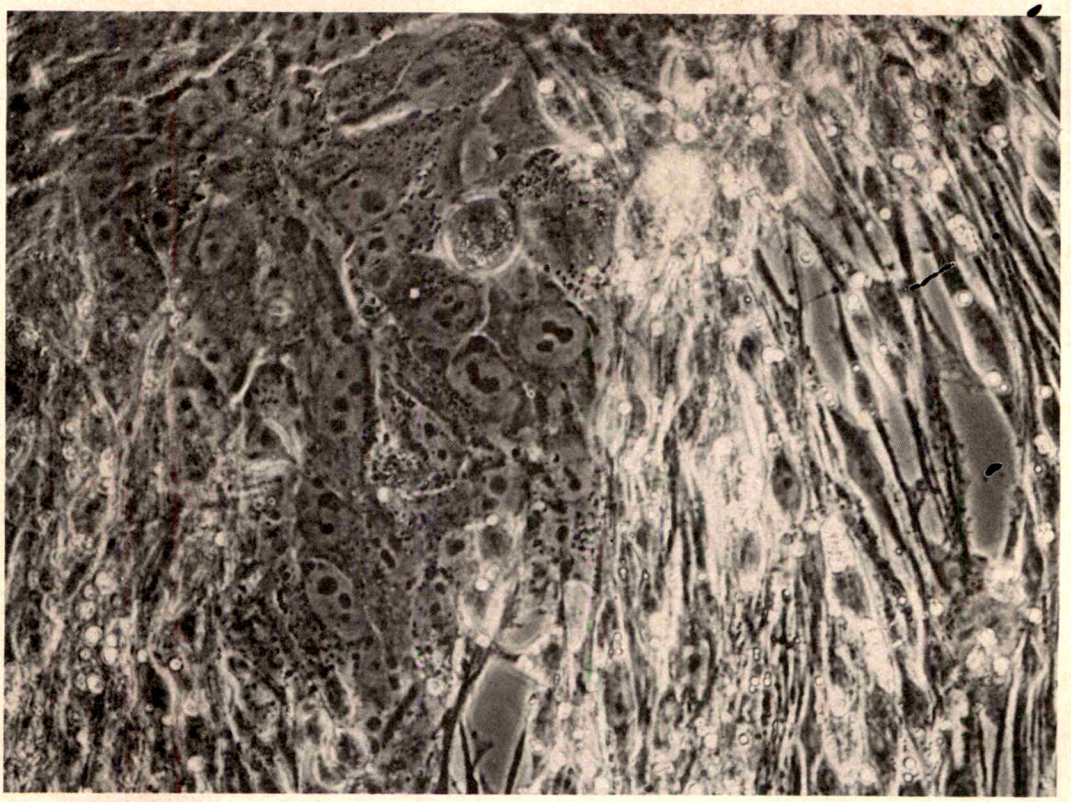


Fig. 5 (Irvine, Mannagh, and Arya). Case 4. Epithelioid and spindle-cell outgrowth in same culture (phase optics ×200).

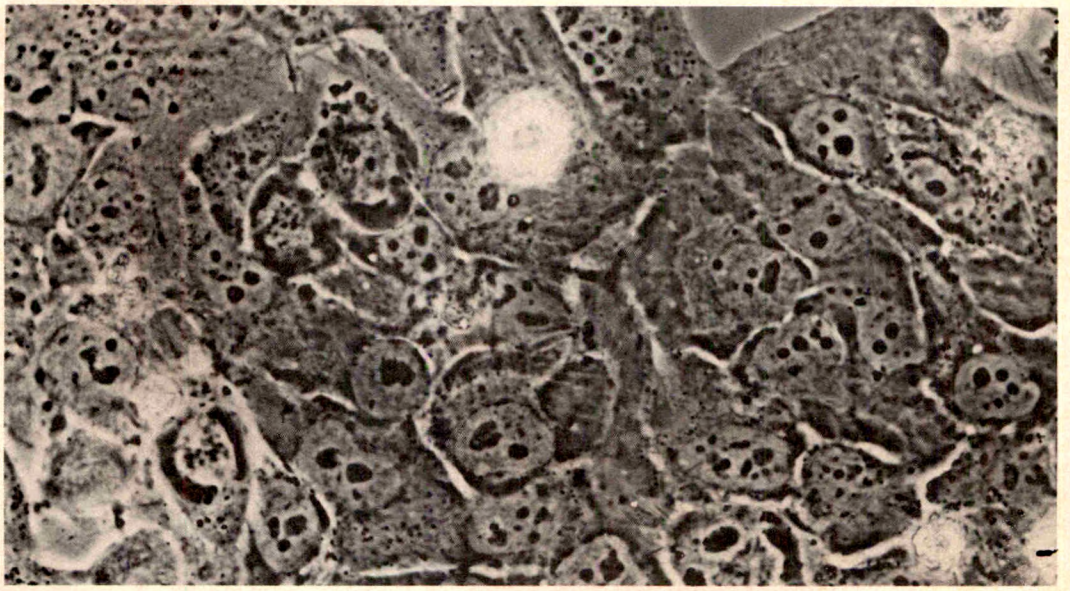


Fig. 6 (Irvine, Mannagh, and Arya). Case 4. Epithelioid cell type in fifth passage (phase optics ×400).

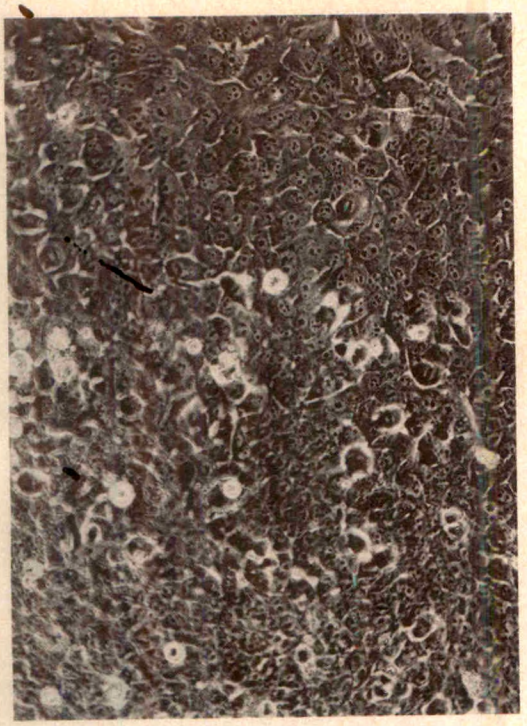


Fig. 7 (Irvine, Mannagh, and Arya). Colony of epithelioid cells from clone (phase optics ×200).

yeast infection 13 months after initial culture. Its mitotic index at transfer 2 was 7.7%.

Discussion

During the course of culturing 52 choroidal malignant melanomas between the years 1965 and 1973 the changes noted in the five cases reported here were not anticipated. This accounts for the incomplete data in Cases 1, 2, 3, and 5, and the like. For example, it was only possible to do generation times on cultures that were still viable.

The reported reversibility in cell type supports the proposition that uveal melanomas arise from the same stem cell and differentiate differently for unknown reasons. The findings support the clinical observations that the cells of epithelioid melanoma divide more rapidly, more frequently and are, therefore, more malignant than spindle-cell types. The reversion of epithelioid to spindle-cell tumors and vice versa makes one wonder whether this correlates with clinical observations of changes in the growth of malignant melanomas. The preponderance of epithelioid cells in that portion of a choroidal malignant melanoma that mushrooms through the lamina vitrea is attributed to tissue pressure becoming less when the lamina vitrea has been disrupted, a hypothesis not supported by the reversible changes noted in tissue culture where the pressure is the same throughout the culture chamber. It may be that the rupture of Bruch's membrane is related to the conversion of slower-growing spindle cells to the more rapidly growing epithelioid type.

The cells becoming epithelioid in subculture often differ in appearance from the epithelioid cells of the original tumor. The latter are characterized by pleomorphism and in varied intensity of staining, whereas the cultured epithelioid cells are usually smaller than those of the primary tumor and tend to be much more uniform in size.

The possibility that the apparent reversibility of cell types represents the preferential growth of one cell or the other from cultures and subcultures that really contain some of both cell types is difficult to exclude. It seems unlikely that this is so in the light of Case 4 where 16 subcultures were epithelioid, the 17th was spindle, and all the subsequent transfers remained epithelioid.

Case 4 remained epithelioid through 96 transfers. The stability of the growth of this tumor with the near constant mitotic index, chromosome heteroploidy, and generation times have led us to consider this to be a true cell line.

Summary

In five cases choroidal malignant melanoma spontaneously converted from epi-

IRIDOCYCLITIS ASSOCIATED WITH JUVENILE RHEUMATOID ARTHRITIS

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The ocular signs of juvenile rheumatoid arthritis (JRA) have been well described.[1–5] We present the clinical histories of 45 patients with chronic iridocyclitis associated with JRA seen in the Uveitis Survey Clinic of the University of California, San Francisco, to emphasize the following: (1) children with mild, limited arthritis are those who develop chronic iridocyclitis; (2) antinuclear antibody (ANA) is frequently present in chronic iridocyclitis associated with JRA; and (3) as presently administered, anti-inflammatory therapy with corticosteroids does not seem to alter materially the course of the JRA-associated ocular inflammation.

The descriptive term "juvenile rheumatoid arthritis" covers a spectrum of clinical syndromes. On the basis of the degree of articular and systemic involvement at the onset of these syndromes, Calabro and Mareschano[6] divided them into three major types (Table 1).

Acute systemic JRA—This form occurs principally in young boys and accounts for 20% of all cases of JRA.[6] It begins with a high fever, a characteristic rash, anemia, lymphadenopathy, hepatosplenomegaly, and pericarditis. Most patients subsequently develop chronic polyarthritis. Still's original description included this type,[7] and the terms "JRA" and "Still's disease" are now used interchangeably. Uveitis has not been reported in patients with this disease.

Polyarticular-onset JRA—Another 50% of cases, most of them in girls, have a polyarticular onset with simultaneous involvement of five or more joints.[6] Despite a low incidence of systemic features, most of these children, like those in the first group, appear to be ill. Although this variant has been called "adult-type onset JRA," serum rheumatoid factor and subcutaneous nodules are rarely found. Schaller, Kupfer, and Wedgwood[3] reported uveitis in a small percentage of cases.

Monarticular-onset JRA—The third type of JRA is monarticular at onset and affects 30% of cases.[6] The incidence is higher in girls than in boys by three to one. Insidious swelling, pain, and stiffness in a large joint, most frequently the knee, are characteristic, and occasionally a small joint in the hand, foot, or elsewhere is affected. These children are apparently healthy and their arthritis responds well to treatment. In most cases it remains monarticular or pauciarticular (four or fewer joints), and rheumatoid factor is absent. Systemic signs are rare, but iridocyclitis is common; Schaller, Kupfer, and Wedgwood[3] found it in 29%

TABLE 1

TYPES OF JRA AND FREQUENCY OF UVEITIS

Types of JRA	% of All JRA	Associated Uveitis
Acute systemic onset	20	Absent or rare
Polyarticular onset	50	Uncommon
Monarticular onset	30	Frequent

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Presented in part at the X Pan American Congress of Ophthalmology, San Juan, Puerto Rico, April 25, 1975.

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of their cases. This, then, is the type of JRA that concerns ophthalmologists and comprises most of the cases discussed in this report.

MATERIAL AND METHODS

From 1956 through 1973, 45 cases of uveitis and JRA were diagnosed in the Uveitis Survey Clinic. Many of the patients had been referred because of their uveitis and only later were diagnosed as having JRA by a rheumatologist on the basis of history, physical findings, and the results of x-ray studies. In some cases, particularly those with monarticular arthritis, arthrocentesis and an analysis of the synovial fluid or tissue were done to exclude joint trauma or infection. Cases of juvenile-onset ankylosing spondylitis, which may appear initially as arthritis of the extremities and are associated with acute iridocyclitis,[4] were excluded.

The uveitis was considered to be related to the arthritis only if no other specific infectious or inflammatory relationship could be established. Several patients were excluded from the series because follow-up examinations showed that they fit into other syndromes, such as sarcoidosis or Behçet's disease. Information on 28 of the 45 patients, based on follow-up examinations made in 1973 in the Uveitis Survey Clinic, or by the patient's local physician, was available for the purposes of this evaluation.

RESULTS

Special clinical characteristics—In agreement with previous reports,[3-6,8-10] most of the patients in the series had mild monarticular or pauciarticular JRA (41 of the 45 patients, Table 2). Among those with monarticular disease, the knee was most frequently affected. In a few patients a small joint elsewhere, even in the larynx, was the initial site. In the three patients with chronic polyarthritis, only one was crippled. One atypical patient apparently had acute systemic JRA. He developed mild iridocyclitis a few weeks after the onset of fever, rash, and arthritis, and extensive medical evaluation led to the diagnosis of JRA. For the past year both his arthritis and uveitis have been inactive.

TABLE 2

IRIDOCYCLITIS AND TYPES OF JRA*

Types of JRA	No. of Patients With Uveitis
Acute systemic JRA	1
Polyarticular JRA at onset	3
Monarticular or pauciarticular JRA at onset	41
Total	45

*Data collected from the University of California, 1956–1973.

Other characteristics of these patients are listed in Table 3. Females outnumbered males by four to one. In most cases the uveitis was eventually bilateral. The onset was often unilateral, however, and for the most part asymptomatic. Some cases showed mild ocular irritation and redness, however, and a few had diminished vision, an abonormal pupil, or strabismus.

Onset—Since the disease was usually asymptomatic, its onset was generally impossible to date. The iridocyclitis was detected by age 6 years in half of the patients (Table 4). In six cases the uveitis

TABLE 3

SPECIAL CHARACTERISTICS OF IRIDOCYCLITIS AND JRA*

Sex distribution	37 females, 8 males
Laterality of uveitis	40 bilateral, 5 unilateral
Duration of uveitis	1–21 yrs (median, 5 yrs)

*Data collected from the University of California, 1956–1973.

TABLE 4

ONSET OF IRIDOCYCLITIS AND JRA*

Age at Onset, yrs	No. of Patients	% of Total No. of Patients
2–6	18	41
7–11	16	35
12–16	5	11
Over 21	6	13

*Data collected from the University of California, 1956–1973.

preceded the arthritis by periods ranging from one to nine years. In the other 39 cases the uveitis followed the onset of the joint disease within a few months or years. In five patients the iridocyclitis was delayed, or at least undetected, until adulthood, the eldest patient in this category being 32 years of age.

Duration—As noted by others,[3–5] the activity of the uveitis seemed to be independent of the activity of the joint disease. Whereas the arthritis tends to disappear in adult life,[11] the iridocyclitis persists: 24 of the 28 patients reexamined in 1973 still had active iridocyclitis, and its known duration ranged from one to 21 years, with the median five years. Eventually most patients had persistent aqueous flare, suggesting that changes in the cells of the aqueous indicate activity. There were extended periods of quiescence however, the longest lasting four years, and whether chronic flare indicates active inflammation or just altered vascular permeability is unknown.

Complications—The overall frequency of complications was similar to that reported elsewhere.[4,5] Of 85 affected eyes, vision in 38% had been reduced to an acuity of 20/200 or less; 49% had some degree of band keratopathy; 61% had posterior synechiae; 58% had cataract; and 22% had glaucoma. A few patients showed macular edema and degeneration, but none had retinal vasculitis or chorioretinitis (Table 5).

TABLE 5

COMPLICATIONS OF IRIDOCYCLITIS AND JRA*

Complications	No. of Eyes	% of Total No. of Eyes
Visual acuity 20/200	32	38
Band keratopathy	42	49
Posterior synechiae	52	61
Cataract	49	58
Glaucoma	19	22

*45 patients, 85 eyes; University of California, 1956–1973.

Therapeutic measures—Currently available anti-inflammatory therapy was relatively ineffective. The experience with corticosteroids is summarized in Table 6. The apparent success of topical corticosteroids in preserving vision is illusory since the group so treated consisted mainly of cases of short duration. As shown in Table 7, the frequency with which visual loss was sustained increased with the duration of the uveitis. In many cases topical corticosteroids seemed to have no effect on anterior chamber cells and flare. The groups treated with corticosteroids orally or by periocular injection tended to be cases of longer duration in

TABLE 6

CORTICOSTEROID TREATMENT OF IRIDOCYCLITIS AND JRA

Treatment Method	No. of Eyes Treated	Visual Acuity Reduced to ≤20/200* No. of Eyes	% of Total No. of Eyes
Topical	33	1	3
Periocular	7	0	0
Systemic	27	13	48

*Eyes with visual acuity of 20/200 before treatment were excluded; University of California, 1956–1973.

TABLE 7

PROGNOSIS OF IRIDOCYCLITIS AND JRA*

Duration of Uveitis, yrs	No. of Eyes	Visual Acuity Reduced to ≤20/200	
		No. of Eyes	% of Total No. of Eyes
1–5	34	11	32
6–10	27	12	45
11–20	13	9	69

*74 eyes; University of California, 1956–1973.

TABLE 8

IRIDOCYCLITIS AND JRA: RESULTS OF CATARACT SURGERY ON 23 EYES*

Visual Acuity 1973	No. of Eyes
20/20	3
20/40–20/100	9
20/200 or less	11

*Data collected from the University of California, 1956–1973.

which the corticosteroids were used because of threatened vision. One might argue that structural damage was already too advanced to permit a fair judgment of these agents, but seven patients were already taking oral prednisone for their arthritis when the iridocyclitis appeared, and the outcome of the ocular disease in these patients was no better than in the group as a whole.

In two cases, cyclophosphamide and azathiaprine were tried but failed to affect the aqueous reaction. Most patients received large doses of aspirin for their arthritis, but this did not apparently affect the anterior chamber signs or the outcome of the uveitis. Other drugs that affect prostaglandin-mediated vascular hyperpermeability were not tried.

Cataract surgery—In view of the prevailing inefficacy of anti-inflammatory therapy, it was encouraging to find the relatively favorable results of cataract surgery. Of 20 eyes subjected to discission-aspiration or extracapsular procedures, 12 had improved visually when last examined in 1973; in three of these the visual acuity was 20/20 (Table 8).

Intracapsular extraction was done on three eyes and went well, but the visual result was poor due to macular degeneration or subsequent inflammation. In all of the successful cases, periocular corticosteroids, and often systemic corticosteroids, were used preoperatively and postoperatively to quell the acute inflammatory response to surgery. Such new instruments as the suction-cutter apparatus were not tried.

Glaucoma surgery—Glaucoma surgery was a difficult problem. Eight eyes were operated on, but in only three was the pressure adequately reduced (to 20 mm Hg or less), and from this small number no conclusions could be drawn as to the best technique to use (Table 9).

DISCUSSION

The reason for the relative frequency of chronic iridocyclitis in association with this type of JRA (monarticular and pauciarticular) is unknown. Schaller and associates[12] suggested the possibility of an underlying infectious process or immune abnormality in these patients since they

TABLE 9

IRIDOCYCLITIS AND JRA: RESULTS OF SURGICAL PROCEDURES FOR GLAUCOMA*

Procedure	No. Successful/ No. Operated
Goniotomy	1/4
Thermal sclerostomy	1/1
Trabeculectomy	1/2
Total	3/7

*Data collected from the University of California, 1956–1973.

found them to have an 88% frequency of serum IgG (ANA) as opposed to 30% frequency in patients with JRA but no uveitis. Since there were no other types of autoantibodies evident, this association with ANA appeared to be specific. In the Uveitis Survey Clinic, the evidence presently suggests that ANA is infrequent in children with chronic iridocyclitis who do not have arthritis (chronic iridocyclitis in young girls).

The role of the ANA in the ocular inflammation is not understood. The patients described by Schaller and associates[12] had no evidence of either systemic vasculitis or immune complex disease, processes often mediated by ANA.

Whatever the cause for the persistent iridocyclitis in JRA, current treatment with corticosteroids is unsatisfactory. The available immunosuppressive agents are dangerous and do not appear to be effective. Our experience in this study suggests, moreover, that their long-term use is unjustified. Only the short-term use of systemic and periocular corticosteroids at the time of intraocular surgery is useful.

Summary

In a study of 45 patients, those with monarticular and pauciarticular juvenile rheumatoid arthritis, and with antinuclear antibodies, were likely also to have chronic, persistent iridocyclitis. In cases where iridocyclitis was present, topical mydriatics were used to prevent formation of posterior synechiae. Topical corticosteroids were used but discontinued if the uveitis failed to respond. Despite the generally poor prognosis for the vision of these patients, surgery for complicated cataract was often successful.

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OCULAR INVOLVEMENT IN BENIGN BOTULISM B

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In 1973 an outbreak of botulism after ingestion of contaminated imported soft cheese struck at least 48 persons in Switzerland.[1,2] Although cheese is unlikely to carry botulin toxin, all case histories pointed to a singular batch of French soft cheese (Brie) which had been allowed to ripen over an exaggerated period of time at the factory and additionally had been subject to unusually high temperatures during transportation. As a result, the fungus rind seems to have consumed all available oxygen, thereby permitting anaerobic growth of *Clostridium botulinum* B within the package. Of these 48 persons, we examined nine within a period of six to 28 days after the onset of symptoms. The patients were followed until disappearance of all complications.

CASE REPORTS

Case 1—A 25-year-old woman suddenly suffered from dizziness and severe near vision disturbance which led to ophthalmic examination. She had an accommodative amplitude of only 1 diopter in each eye as well as moderate bilateral mydriasis and a Schirmer I test of 16 reps 10 mm. There was no paresis of an extraocular muscle or blepharoptosis. She complained of an extremely dry mouth and of difficulty in swallowing dry food. There was some general fatigue but no suspicion of muscular weakness. Careful questioning revealed that she had ingested Brie cheese a few days earlier. The mouse test for botulism was positive (identified as type B).*

Further examination revealed decreased salivary secretion measured by cannulating the parotid duct. There were no electromyographic changes suggesting a neuromuscular defect. The administration of botulin antitoxin did not seem to alter the clinical course. On the 33rd day after onset of symptoms, guanidine was administered by mouth. Despite the fact that the patient still complained of paresthesias and nausea, her accommodative amplitude returned to normal 48 hours later. At 230 days the patient was free of complaints, except for dry-eye symptoms after exposure to wind. This was alleviated by wearing protective glasses.

Case 2—A 41-year-old man noticed constipation 12 hours after ingestion of soft cheese. He continued his usual work but became generally weak and complained of an extremely dry mouth with trouble in swallowing. On the seventh day of his illness his near vision became blurred. The patient was seen 23 days after onset, when a sluggish pupillary reaction was noticed. The patient complained of dry eyes, and a Schirmer I test of 6 reps 12 mm was found. Salivary production was subnormal; the electromyogram revealed no neuromuscular defect. The mouse test was positive and the toxin was again identified as type B. A single injection of polyvalent antitoxin was administered on the 35th day. A second mouse test was reported as negative. Only after administration of guanidine by mouth did the patient report immediate and complete improvement of near vision. After 200 days there were still dry-eye symptoms, despite a Schirmer I test of 22 reps 26 mm in both eyes.

Case 3—This 21-year-old woman complained of a sudden loss of near vision, which was preceded by obstipation for seven days. She, too, had ingested Brie about one week before the onset of her visual troubles. There was no diplopia detectable; the pupillary reflexes were sluggish. She complained of slight nausea, obstipation, and dry mouth. A positive mouse test to botulism confirmed the diagnosis three weeks after onset. A single dosage of polyvalent botulin antiserum (50 mm injected intramuscularly in 10-mm doses on the same day at different sites) was administered but this was not effective. The clinical symptoms including the accommodative paresis disappeared suddenly one month after the ingestion of the toxin.

In the remaining six patients the clinical picture was essentially the same (Table). The accommodative deficiency was the most striking symptom, especially in the younger patients who had no corrective lenses.

RESULTS

The latency between ingestion of contaminated food and onset of symptoms

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*The mouse test consists of intraperitoneal injections of mice with the patient's serum. This will produce death of the mice in one to four days if significant amounts of botulin toxin are present. The immunologic type of toxin can be identified by appropriate mouse protection tests utilizing specific antitoxins.

TABLE

SYMPTOMS IN NINE PATIENTS WITH BENIGN *C. botulinum* B INFECTION*

Symptoms	Patient No. 1	2	3	4	5	6	7	8	9	Total
Blurred vision	+	+	+	+	+	+	+	+	+	9
Dry mouth	+	+	+	+	+	+	+	+	+	9
Constipation	−	+	+	−	+	+	+	+	−	6
Dizziness	+	+	−	−	+	+	−	+	+	6
Abdominal cramps	−	+	+	−	−	−	+	+	−	4
Nausea/vomiting	−	−	+	+	+	−	−	+	−	4
General weakness	+	+	−	−	−	−	−	−	+	3
Apathetic behavior	−	+	−	−	−	+	−	−	+	3
Orthostatic hypotension	−	+	+	−	−	−	−	−	−	2
Impaired micturation sexual function	−	+	−	−	−	−	−	−	−	1

*Present, +; absent, −.

could be determined in only five of nine patients. The average time was 37 hours. The ocular symptoms were sometimes preceded by nausea and vomiting. All patients had marked accommodative paresis. In two patients there was no accommodation. In the other seven the accommodative amplitude did not exceed 3 diopters. Full mydriasis was observed in only one patient, while another showed sluggish pupillary reactions. Obstipation and general dizziness were present in six patients. All nine patients complained of dry-eye and dry-mouth symptoms. The Schirmer I test was carried out in all subjects with inconsistent results. The measurement of salivary production of the parotid gland gave subnormal values in four patients. Electromyography, performed in four patients, revealed no defect of neuromuscular transmission and the phenomenon of facilitation could not be observed.

The mouse test was positive in five patients. The earliest negative result was obtained on the 17th day of illness, the latest positive result on the 28th day. Specific treatment with antitoxin was given to five patients, without effect. Guanidine therapy produced striking accommodative results in two patients. Side effects of guanidine hydrochloride (500 mg three times daily) were distally located paresthesias and occasional diarrhea.

DISCUSSION

Botulism infections due to a toxin-producing strain of *C. botulinum* are fortunately rare. Most occur through ingestion of poisoned food. Serologically six different strains can be distinguished (A, B, C, D, E, and F). Only A, B, and E are of clinical importance. The severity of clinical manifestations, including death, may differ considerably based not only upon the amount of ingested toxin, but also on the toxin type in general. Types B and E are less toxic than type A.[3–10] All clinical symptoms are explained by diminished release of acetylcholine at the cholinergic transmission sites of the peripheral nervous system.[11]

Occasional reports dealing with less severe forms which still manifest pronounced autonomic dysfunction have appeared recently.[1,2,5–10] In the present study all nine cases of botulism B were characterized by a benign, but strikingly protracted, symptomatology. Accommodative pareses, pupillary anomalies, diminution of secretion, and obstipation were the main symptoms. All of these were consistent with peripheral cholinergic dysfunction. Dizziness, nausea, orthostatic dysregulation, and abdominal cramps were more difficult to explain. They might well have been related to the ingestion of the botulin toxin itself.[12]

Descriptions of *C. botulinum* A intoxication invariably stress that autonomic dysfunction is not necessarily a factor in the general symptomatology.[13–15] This is in contrast to *C. botulinum* B intoxication, where autonomic dysfunction appears to produce the leading symptoms and the patients do not usually demonstrate a neuromuscular deficit. Possibly the auto-

nomic cholinergic transmitter system has a pronounced susceptibility to *C. botulinum* B toxin.[16] The generally lower toxic potency of the B toxin in comparison to the A type is well known,[17] but would not itself seem to be a sufficient explanation for the different clinical symptomatology. Duchen[18] further elucidated the striking difference between the two strains.

As far as treatment is concerned, we feel that there is no indication for administering polyvalent *C. botulinum* B antitoxin in a case with minor symptomatology. Sheelo,[19] however, stressed that his patient was aware of subjective improvement after the injection of botulin antitoxin which was given simultaneously with guanethidine (Ismelin) treatment. A striking beneficial effect upon the autonomic disturbances was produced in our two patients who were treated with guanidine hydrochloride, 500 ml three times daily, as advocated by Cherington and Ryan.[20,21] The physician should, however, be familiar with some of the contraindications such as diarrhea and parestheses.

SUMMARY

In nine cases of botulism B infection due to food poisoning acute onset of accommodation paresis, mydriasis, and dry-eye symptoms were the prominent clinical findings. Impairment of salivary secretion as a further effect upon cholinergic autonomic innervation was detectable for months. Guanidine treatment had a beneficial effect, whereas administration of antitoxin in the late and benign form was not effective.

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UVEITIS AND RETICULUM CELL SARCOMA OF BRAIN WITH BILATERAL NEOPLASTIC SEEDING OF VITREOUS WITHOUT RETINAL OR UVEAL INVOLVEMENT

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The occurrence of ocular complaints attributable to uveitis has been well documented in both cerebral[1-6] and systemic[5-10] reticulum cell sarcomas. Vitreous clouding, the most prominent clinical finding in many of these cases, has been shown histopathologically in several cases to be secondary to neoplastic involvement of the retina or uvea with seeding of tumor cells or inflammatory cells into the vitreous, or both.[1,2,5,6,10] The patient described by Givner[1] had had uveitis in the right eye and ophthalmoscopic evidence of multiple subretinal tumors in the left eye. By the time she died (of reticulum cell sarcoma), the tumors in the left eye had regressed, leaving only subretinal scars; histopathologic study of the right eye, which had had a cloudy vitreous, revealed neoplastic cells only in the vitreous.

This report describes the case of a patient with bilateral uveitis and clouding of the vitreous who had been observed for over four years before her death from cerebral reticulum cell sarcoma. Histopathologic examination of the eyes at autopsy revealed myriad neoplastic cells in the vitreous of both eyes but no neoplastic infiltration in any other ocular tissue.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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CASE REPORT

A 65-year-old white woman was first seen by an ophthalmologist for a routine eye examination in May 1969. At that time her visual acuity was 20/25 in both eyes, and she had no visual complaints. Ophthalmoscopic examination with the fundi dilated revealed only a few macular drusen bilaterally. She returned 18 months later complaining of decreasing vision in both eyes. Visual acuity was RE: 20/50; LE: 20/40. Examination revealed myriad fine vitreous opacities bilaterally, but no retinal lesions were observed. There were no other signs of ocular inflammation, and general physical examination disclosed no abnormalities. After about three months the vitreous clouding rapidly became worse, visual acuity of both eyes deteriorated to light perception, and the fundi could not be visualized. Systemic corticosteroids were given for one week, after which time the patient complained of thirst, flushing, fever, mental confusion, and dryness of the skin. She was hospitalized for several days in February 1971, and these systemic symptoms cleared with cessation of the corticosteroid therapy and administration of fluids intravenously. Visual acuity remained poor, generally 20/200 or less in both eyes.

In May 1971 she was referred to a larger medical facility for a complete evaluation because of increasingly severe headaches, mental confusion, fever, ataxia, and vomiting. Her husband described personality changes, especially paranoia and visual hallucinations. Shortly after admission, her mental status deteriorated, and she was comatose for approximately two weeks. A clinical diagnosis of viral encephalitis was made.

During that admission, studies of cerebrospinal fluid revealed normal pressures, normal protein and glucose levels, and a lymphocytosis of 13 cells/mm^3. India-ink preparations for yeast, as well as bacterial and viral cultures, gave negative results. Results of serologic tests for syphilis on blood and cerebrospinal fluid were negative. Titers for herpes virus were negative, as were cold agglutinins and febrile agglutinins. Roentgenograms of the skull, brain scan, right and left carotid arteriograms, and a pneumoencephalogram also gave negative results. Her electroencephalogram was diffusely abnormal.

The patient was sufficiently improved one month after admission to be placed in a nursing home. In August 1971 she was readmitted to the hospital with an abscess in the right parotid area. After drainage of the parotid abscess, she was afebrile but manifested fluctuating mental status over the next several weeks. Histopathologic examination of tissue ob-

tained from the drainage site revealed only chronic inflammation. Personality changes persisted thereafter, and she continued to have mild difficulty with her gait. Anemia of moderate degree, thought to be of nutritional origin, was noted. Repeated studies of cerebrospinal fluid showed normal pressures, only 2 lymphocytes/mm^3, and normal levels of glucose and protein.

After she returned to her home, frequent ophthalmologic examinations were made, but there were no significant changes in her vision or in the ocular findings until August 1972, when minimal flare and a few fine keratic precipitates were noted bilaterally. Topical corticosteroids provoked a rise in intraocular pressure, which subsided upon withdrawal of the drug. Mild anterior uveitis persisted until March 1973, but this later subsided. Flare and keratic precipitates were again noted bilaterally between July and December 1973. In January 1974, she developed difficulties in her gait, with falling to the right, and then a complete right hemiplegia. A neurosurgical consultant found evidence of a mass in the left thalamic region. She died in April 1974, almost five years after the onset of visual complaints and about three years after her personality changes and initial signs of organic cerebral disease.

A complete autopsy was performed.

Results

No peripheral lymphadenopathy or hepatosplenomegaly was present. Abnormal findings were confined to the brain and eyes. A hemorrhagic, partially necrotic tumor measuring 7 cm in diameter replaced the left thalamus and compressed the left lateral ventricle. It was composed of poorly differentiated mononuclear cells in a conspicuous perivascular distribution, typical of reticulum cell sarcoma (microglioma) (Fig. 1).

The left eye was received intact for complete examination at the Armed Forces Institute of Pathology. Significant findings included clouding of the vitreous and small clumps of grayish-white material along the base of the vitreous. A few retinal hemorrhages were present. On histopathologic examination, the vitreous was seen to contain numerous atypical mononuclear cells with large nuclei that showed infoldings of the nuclear membranes and prominent nucleoli (Fig. 2). Many of these immature cells appeared to have undergone karyorrhexis, karyolysis, and necrosis persisting as "ghost" cells. The iris contained a few chronic inflam-

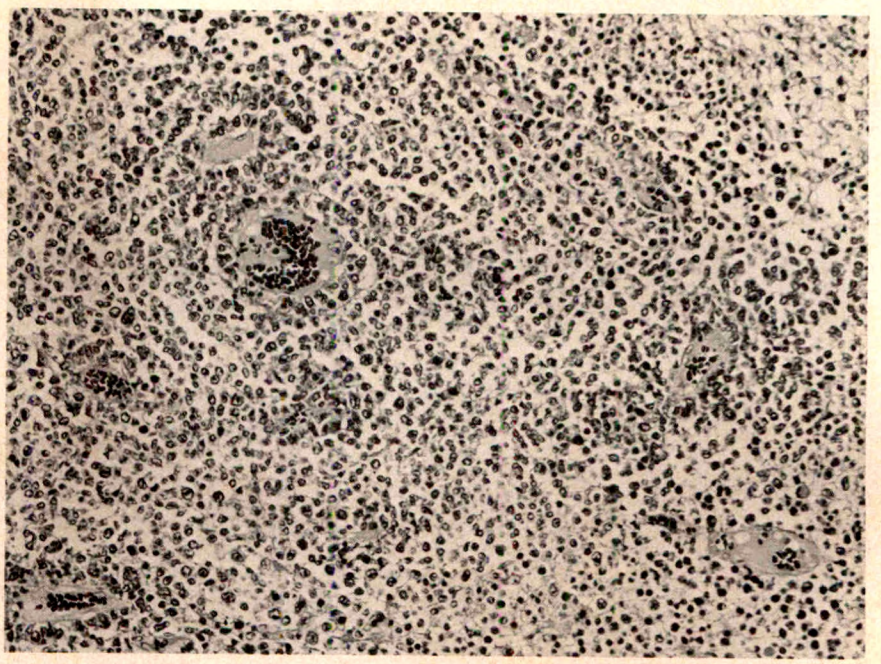


Fig. 1 (Minckler, Font, and Zimmerman). Reticulum cell sarcoma (microglioma) of brain (hematoxylin and eosin, X225; AFIP Neg. 74-11563).

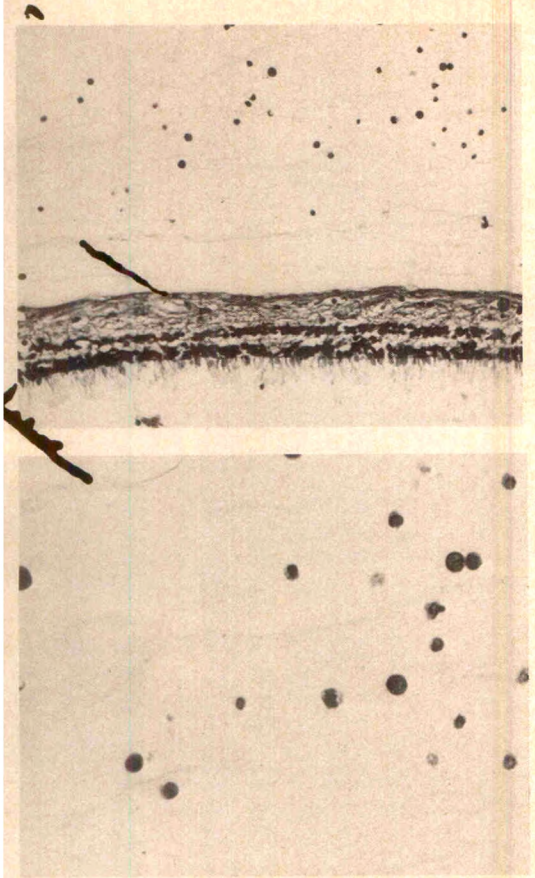


Fig. 2 (Minckler, Font, and Zimmerman). Top, Mononuclear cells in the vitreous of the left eye. The peripheral retina shows thinning of the inner nuclear layer and slight reduction in the number of ganglion cells (hematoxylin and eosin, X180; AFIP Neg. 74-11570). Botton, Higher magnification of the atypical mononuclear cells in the vitreous (hematoxylin and eosin, X395; AFIP Neg. 74-11572).

matory cells. The retina was unremarkable except for a disciform chorioretinal scar involving the macular region (Fig. 3). Focal collections of chronic inflammatory cells were present throughout the choroid. Areas of atrophy with focal demyelination corresponding to the macular scar were present in the optic nerve. Multiple sections through the center of the eye and through both calottes revealed no tumor cells in the uvea or retina.

The original slides and additional sections prepared from the paraffin blocks of the right eye* showed atypical mononuclear cells in the anterior vitreous (Fig. 4) similar to those found in the left eye. The right macula, however, was normal. No uveal or retinal involvement by tumor was identified.

Several consultants concurred that the cells in the vitreous of both eyes were cytologically malignant and morphologically similar to those seen in the reticulum cell sarcoma of the brain.

Discussion

This patient's clinical course was typical of that described for reticulum cell sarcoma of the central nervous system with ocular involvement.[2,3,5,6] In many of these cases, the patients initially complained of decreased vision secondary to vitreous clouding believed to be due to uveitis long before involvement of the brain was evident. All cases have involved middle-aged or older individuals, many of whom had bilateral ocular manifestations. The uveitis has varied in severity from mild to severe and has occasionally been associated with "mutton fat" keratic precipitates. Most often, the uveitis has been manifested primarily as a vitreous haze frequently obscuring visualization of the fundus. Involvement of the anterior segment has typically been slight. While uveitis has preceded neurologic symptoms in most of the reported cases, the reverse sequence can also occur, as in three cases reported by Klingele and Hogan[5] and in two others on file in the Registry of Ophthalmic Pathology. Various retinal infiltrates, chorioretinal lesions, and subretinal masses have been seen clinically, and these have often been confused with inflammatory disease.[1–3,5,6,11] Retinal and vitreous hemor-

*Slides and blocks from the right eye, which had been sent to the University of Cincinnati for pathologic examination, were obtained from Joseph Ginsberg, M.D., and Abbot Spaulding, M.D.

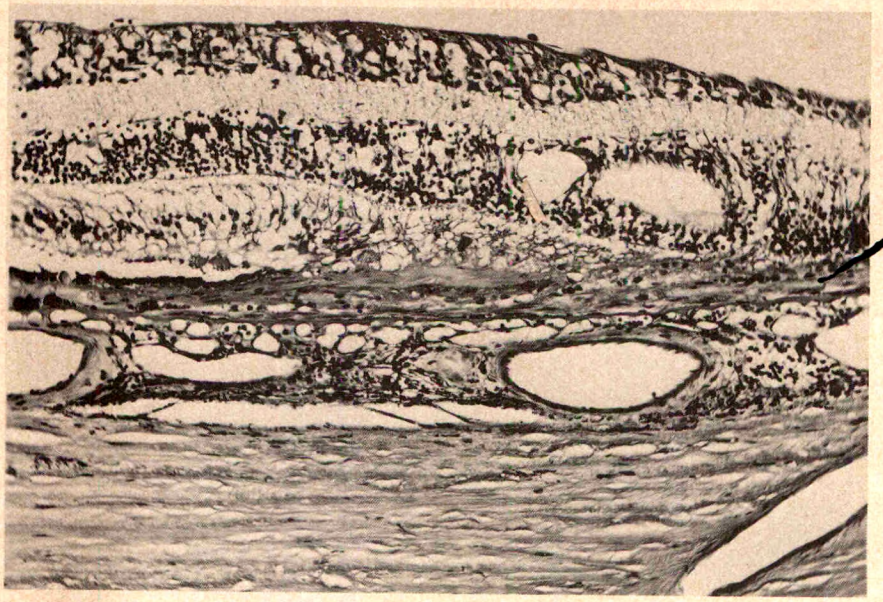


Fig. 3 (Minckler, Font, and Zimmerman). Chorioretinal scarring involving the macula of the left eye (hematoxylin and eosin, X115; AFIP Neg. 75-5494).

rhages and exudative retinal detachments have occurred. Papilledema has been ascribed to (1) direct involvement of the optic disk by tumor, (2) hypotony associated with uveitis, and (3) increased intracranial pressure related to the cerebral neoplasm.[3] Intraocular pressure has frequently been elevated,[2,5,6,10] and in some patients the pain associated with advanced glaucoma has been the main reason for enucleation of the globe.

The histopathologic findings in this case are most unusual in that in each eye only the vitreous body was infiltrated by tumor cells and that reticulum cell sarcoma was not observed in the retina or uveal tract of either eye. Among previously reported cases subjected to histopathologic examination, only two had similar neoplastic involvement limited to the vitreous.[1,12] The right eye of Givner's patient[1] had neoplastic cells only in the vitreous. In the original description of the left eye in the case recorded by Nevins, Frey, and Elliott,[12] involvement of the vitreous by the reticulum cell sarcoma was not described, but our review of the sections showed neoplastic cells in the vitreous similar to those described in our present case, and no involvement of the retina or uvea. In all other reported cases with neoplastic cells in the vitreous, tumor had also involved the retina or the choroid, or both; but we know of another, yet unpublished case similar to ours. At the 1974 meeting of the Verhoeff Society, Myron Yanoff presented the case of an elderly man who had had bilateral opacification of the vitreous before developing signs of a reticulum cell sarcoma of the brain. Both eyes studied post mortem had neoplastic cells only in the vitreous.

Chorioretinal scarring, sometimes described as a disciform area of macular degeneration, has been observed in a number of cases, including the present one.[1,2,5,6,11,12] One might be inclined to consider this a coincidental finding attributable to aging, since the patients are typically beyond middle age. Possibly, however, these lesions also represent sites of previous involvement by the reticulum

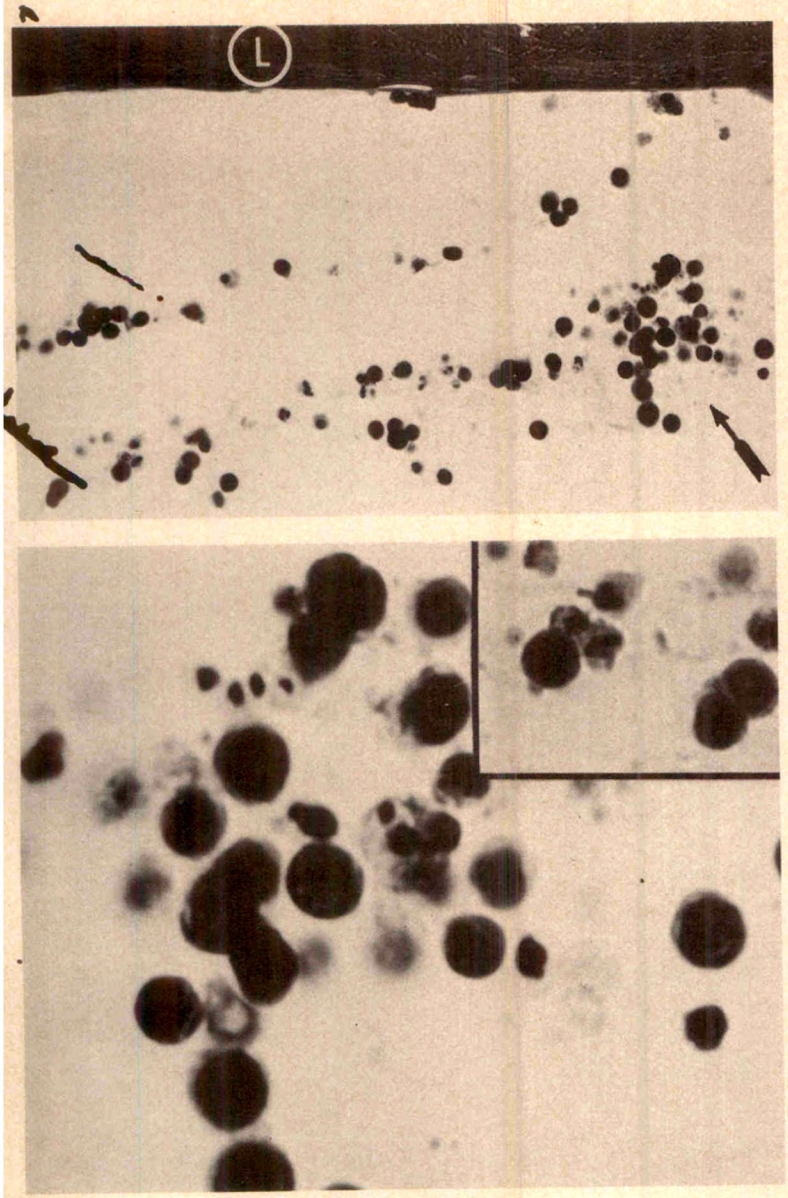


Fig. 4 (Minckler, Font, and Zimmerman). Top, Clumps of large mononuclear cells (arrow) in the anterior vitreous of the right eye, adjacent to the posterior lenticular surface (L). Several necrotic "ghost" cells are present (hematoxylin and eosin, X300; AFIP Neg. 75-1489). Botton, Higher power of area (arrow) in Figure 4, top, shows cytologic features of the neoplastic mononuclear cells (hematoxylin and eosin, X1,300; AFIP Neg. 75-1490). Inset shows one of the mononuclear cells in mitosis (hematoxylin and eosin, X900; AFIP Neg. 75-5490).

cell sarcoma. Several observations suggest this interpretation. First is the curious fact that in this disease there is a remarkable tendency for the neoplastic cells to form a mass that separates the retinal pigment epithelium from Bruch's membrane.[2] This may be seen even in the absence of neoplastic infiltration of either the choroid or the retina. Second are the observations made in the cases described by Givner[1] and Gass.[11] Initial examinations made in those two cases had led to the discovery of large, prominent subretinal tumors that subsequently disappeared (possibly attributable to corticosteroid therapy), leaving behind areas of chorioretinal scarring. In both cases postmortem examination revealed fibrous plaques between the choroid and the sensory retina. In Givner's[1] case the largest

lesion was situated in the region of the macula, while in the case illustrated by Gass[11] the lesions were more peripheral. The uveitis in patients with ocular involvement in reticulum cell sarcoma has generally been resistant to topical and systemic corticosteroids, perhaps because only the inflammatory component responds to therapy. At least two patients have developed systemic manifestations of reticulum cell sarcoma only a few weeks after beginning to receive systemic corticosteroid therapy (according to a personal communication from Michael Hogan, April 1975).

Henry and associates[13] postulated that the cells in malignant lymphoma of the central nervous system originate from pluripotential primitive fixed mesenchymal cells located in the perivascular tissues. While we believe neoplastic reticulum cells probably invade the vitreous by direct migration from the retina or uvea, they could conceivably also arise from hyalocytes in the vitreous. This possibility of the origin of neoplastic cells in the vitreous seems unlikely, however, because the tumor cells in these cases are typically dispersed and have not formed nodules or large aggregates even after several years, as in the present case.

Although the systemic and cerebral types of reticulum cell sarcoma are cytologically identical,[13,14] even at the electron microscopic level,[15] they tend to have different patterns of ocular involvement. As pointed out by Vogel and associates[2] and by Klingele and Hogan,[5] systemic reticulum cell sarcoma, when it secondarily affects the eye, tends to be associated with lesions in the uveal tract, while in primary reticulum cell sarcoma of the central nervous system there appears to be a tendency for lesions to develop in the sensory retina, vitreous, and between the choroid and retinal pigment epithelium.

In keeping with the desirability of establishing a definitive diagnosis early, it would seem justified to utilize vitreous or aqueous aspiration for cytologic examination of patients with uveitis of unknown origin, especially when associated with cerebral symptoms, to exclude reticulum cell sarcoma.[5] Also, cytologic examination should be performed on cerebrospinal fluid. In retrospect, the "lymphocytes" described in the cerebrospinal fluid of this patient three years prior to death may have been tumor cells. Certainly ophthalmologists, who are likely to see these patients first, should consider the possibility of reticulum cell sarcoma when confronted with middle-aged or older patients presenting a recent or long-standing uveitis associated with cerebral symptoms. When cerebral or systemic reticulum cell sarcoma is diagnosed early, radiation therapy may significantly prolong the life of the patient and ameliorate symptoms.[5,13]

Summary

A 65-year-old woman had been observed for more than four years with bilateral chronic nongranulomatous uveitis and vitreous clouding of unknown cause. Her death was from reticulum cell sarcoma of the brain (microglioma). Both eyes were obtained post mortem. Histopathologic examination revealed malignant cells in the vitreous of both eyes, but no other tumor was demonstrable in the ocular tissues. Reticulum cell sarcoma should be suspected in middle-aged or older persons with chronic unilateral or bilateral uveitis of unknown cause who develop cerebral manifestations during the course of the disease.

Acknowledgments

We thank Robert Buten, M.D., George Tanner, M.D., and Charles L. Stephens, M.D., for the clinical data and autopsy reports they provided.

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A NEW MUCOLIPIDOSIS WITH PSYCHOMOTOR RETARDATION, CORNEAL CLOUDING, AND RETINAL DEGENERATION

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A variety of severe inherited systemic diseases are due to the accumulation of polysaccharides loosely associated with lipid or protein (glycogen, hyaluronic acid) or covalently bound to a polypeptide chain (glycosaminoglycans and glycoproteins) or ceramide (glycolipids).[1] Initially, the accumulation of abnormal compounds in body tissues was considered to be the result of an excessive rate of synthesis. Hers,[2] however, demonstrated that type II glycogenosis was due to the absence of a lysosomal hydrolase. Thereafter attention was directed to the possibility that a genetic alteration of a lysosomal hydrolase caused a special type of inborn error of metabolism specifically affecting intralysosomal digestion. Subsequent studies then indicated a deficiency of lysosomal enzymes responsible for the intracellular catabolism of various materials containing polysaccharide. Since 1970 there has been a remarkable increase in the understanding of these hereditary disorders; both the enzymatic deficiency and the stored compound have been identified in many.

Although the basic abnormalities in many of the inherited disorders of glycolipid, mucopolysaccharide, and glycoprotein metabolism have been identified, several abnormalities appear to be clinically related but are not characterized biochemically. These have been called mucolipidoses[3] although this is clearly a misnomer since the degree of storage of lipid or mucopolysaccharide in the liver or brain is minimal.[1] Several clinical entities have been demonstrated; the first is known as I-cell disease[4,5] based on the many inclusion bodies (lysosomes packed with storage material seen in fibroblasts cultured from these patients). We describe a patient with this disorder who is exceptional in surviving until his 23rd year, having clouding of his corneas and extensive retinal degeneration.

CASE REPORT

This 23-year-old man was born Feb. 25, 1953, and was first seen here April 13, 1954 because of an inguinal hernia and slow psychomotor development. The patient had two normal sisters, 11 and eight years older; his mother had a spontaneous abortion before gestation of each of these sisters. During his gestation, a toxic goiter was removed from his mother during the second month of pregnancy and a general anesthesia was used. Subsequent pregnancy and delivery were uneventful.

The child's development appeared to be normal until he was 5 or 6 months of age when generalized retardation was noted. At 13 months of age, a generalized hypotonia was present with brisk deep reflexes. He did not use words, recognize his parents, or stand without support. The pediatric neurologist thought the child had a double spastic hemiparesis with congenital hypotonia, despite the apparent contradiction of terms. A left esotropia was present. No corneal abnormality was noted.

At 26 months of age, he was able to stand with help. The hypotonia and spasticity persisted. The esotropia was unchanged. The parents had first noted severe corneal clouding several months earlier.

The clouding was variable and appeared as a peculiar smoky gray-brown haze. It involved mainly the anterior stroma and extended to the corneal periphery and resembled the opacity seen in Hurler's disease. Some days the cornea was nearly clear and the iris and pupil could be seen distinctly. Crying caused the cornea to become more opaque. The opacities consisted of minute dots involving particularly the anterior stroma. In the left eye in the

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Presented at the 111th meeting of the American Ophthalmological Society, the Homestead, Virginia, May 30, 1975.

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10 o'clock meridian there was a coalescence of these dots causing a more severe opacity than elsewhere in the cornea.

The pupils reacted to light and were equal. Intraocular pressure (Schiøtz) was 18 mm Hg in each eye. The corneal diameters measured 10.5 mm in each eye. The optic disks, retinal vessels, and maculae were normal.

A variety of compounds were instilled in the conjunctival sac in attempts to clear the corneas. None were successful, although the corneal clouding continued to vary in severity. There were intermittent episodes of severe corneal pain, the cause of which was never found.

When he was 14 years old gingival bleeding developed but this was corrected with administration of ascorbic acid, and the patient's personal physician attributed it to subacute scurvy. The patient was again extensively examined at this time (1967). Examination indicated a truncal ataxia combined with muscular hypotonia of the extremities with intact deep reflexes. Although he was small, his facies were normal with large ears set low on his skull (Fig. 1). He could make simple sounds, but could not form understandable words. Vision was grossly deficient, but hearing appeared normal.

Visual acuity was estimated at finger counting at 2 feet. Intraocular pressure was normal. The esotropia was less marked than previously. The corneal clouding was severe centrally, while the periphery appeared grossly clear; however, biomicroscopic examination indicated the periphery was hazy with ill-defined, dot-like material in all layers. The pupils reacted sluggishly to light. Indirect ophthalmoscopy indicated the disks were atrophic and hypoplastic and blood vessels could not be seen. No gross abnormality in the macular regions was noted. A small clump of pigment was present in the peripheral fundus of the left eye. The scotopic and photopic electroretinogram was extinguished. Several laboratory studies indicated no abnormalities. Hematologic studies indicated normal white blood cells without abnormal granules present intracellulary. The erythrocytes were normal in shape, size, number, and hemoglobin content. Chromatographic analysis for amino acids of urine collected for 24 hours indicated no abnormalities. Mucopolysaccharide excretion was normal. Phytanic acid was not present in the urine. By studying a 96-hour sample of peripheral blood, a normal male karyotype was found. According to Janet D. Rowley, M.D.: "The Y chromosome is as large as an E18 which is the upper limit of normal size for this chromosome. Large, sometimes displaced, satellites are noted in more than half of the photographed metaphases, but this is probably a normal variant. Prominent satellites are present on one D and one G chromosome" (unpublished data).



Fig. 1 (Newell, Matalon, and Meyer). Patient at 14 years of age. His stature and facies were small with prominent ears set low on his skull.

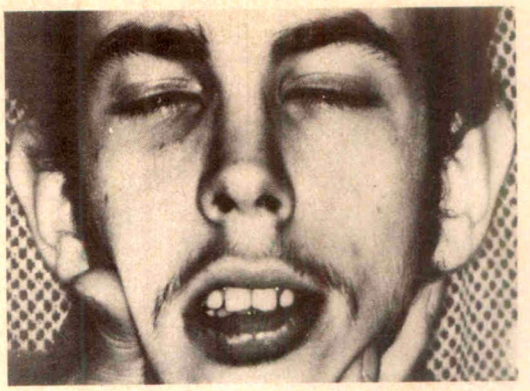


Fig. 2 (Newell, Matalon, and Meyer). Patient at 21 years of age. He was unshaven, thin, and appeared younger than his years. Except for the prominent ears, there was no facial abnormality.

Roentgen-ray examination of the skull, optic foramina, chest, trunk, and extremities indicated no abnormalities. There was slight but insignificant bony growth retardation of the left wrist. The skeletal structures were consistent with 11 years of age as contrasted with a chronologic age of 14 years.

According to the audiologist, hearing appeared normal and the child "could hear soft speech."

Using frozen sections, the conjunctival biospy demonstrated no abnormality with elastic tissue stains for acid mucopolysaccharides and PAS stain.

The findings at this time were mental retardation, ataxia, spasticity combined with atonia, retinal degeneration, and corneal opacification. We concluded this was a metabolic abnormality of an unknown type, comparable to some of the lipidoses.

He was extensively examined again in 1974. There was little change in the physical examination since 1967. Physical examination indicated a thin-framed man, 5 feet 2 inches tall and weighing 115 pounds. He was unshaven and appeared younger than his years (Fig. 2). He could not walk more than a few steps. There was marked mental retardation and he made simple sounds, but did not form words. He was aware of his parents. There was severe truncal ataxia with the curious combination of hypotonia,

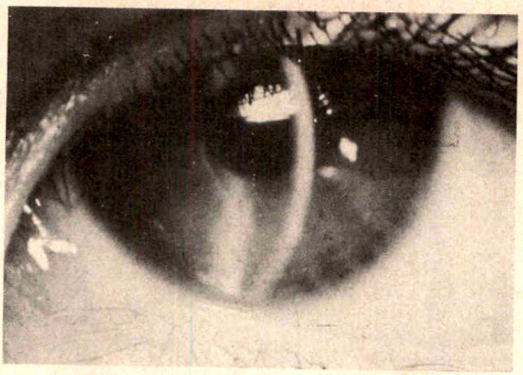


Fig. 3 (Newell, Matalon, and Meyer). The cloudy cornea at 21 years of age. The pupil and iris pattern could be seen, but the haze was severe enough to preclude observation of fundus detail.

spasticity, and normal deep reflexes. Laboratory tests showed no abnormality.

The corneas (Fig. 3) did not appear as cloudy as earlier, but we could not see any fundus details by using either direct or indirect ophthalmoscopy. Only a red reflex could be seen through the clouded cornea. We estimated visual acuity as counting fingers at 2 or 3 feet. The pupils reacted to light sluggishly. The electroretinogram was again extinguished.

On April 11, 1974, using general anesthesia, we removed a small portion of conjunctiva from the right corneoscleral limbus. The tissue was placed immediately in 2% glutaraldehyde. A skin punch was used to remove skin from the right forearm for tissue culture.

The conjunctival specimen was fixed in 2% glutaraldehyde for 12 hours. It was postfixed in 2% osmium tetroxide for one hour; dehydrated through graded ethanol; passed through propylene oxide and ultimately embedded in Epon. Plastic blocks were thin-sectioned using a diamond knife, mounted on an LKB ultramicrotome (400 to 600 nm), stained with uranyl acetate and lead hydroxide, and viewed with an electron microscope. Other sections were stained with toluidine blue and eosin.

RESULTS

Light microscopy indicated small dots of heavy-staining material that, on electron microscopy, was shown to be inclusion material (Fig. 4).

Electron microscopy—Electron microscopy indicated numerous epithelial cells filled with single-membrane-limited vacuoles, 285 to 575 nm in diameter. Many of the vacuoles appeared empty, while others contained membranous inclusions and a polymorphous discrete staining material. The membranous material filled

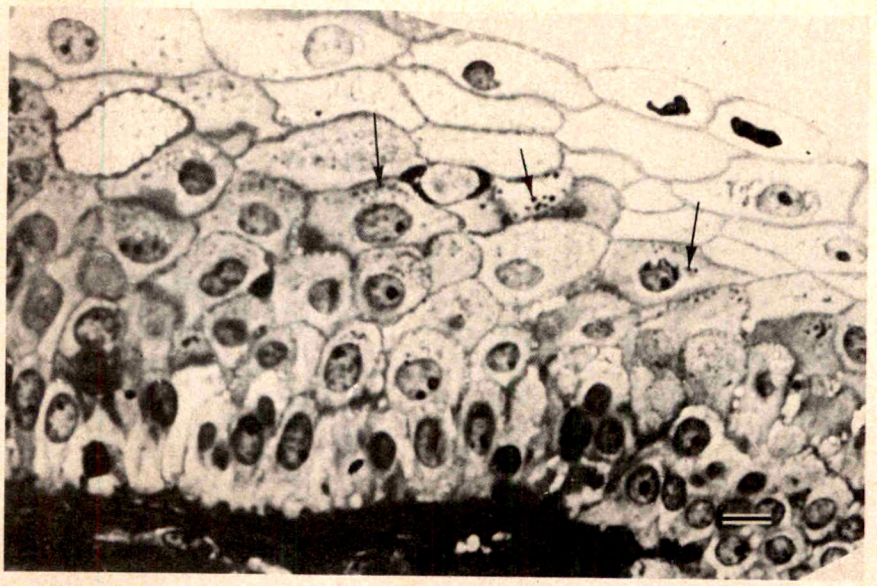


Fig. 4 (Newell, Matalon, and Meyer). One- to two-micron thick sections of conjunctiva were embedded in Epon. The black punctate dots (arrows) were present in variable numbers in nearly every cell. There was a markedly variable degree of staining of the dots. On electron microscopy, dots were inclusion bodies. Bar gauge = 10 μ (toluidine blue, ×500).

some cells nearly completely (Fig. 5), while in others it appeared limited to the periphery. These membranous lamellae appeared largely concentric (Fig. 6) and no periodicity was evident. The vacuoles appeared randomly scattered without any particular cell material. A rare inclusion appeared to be extracellular.

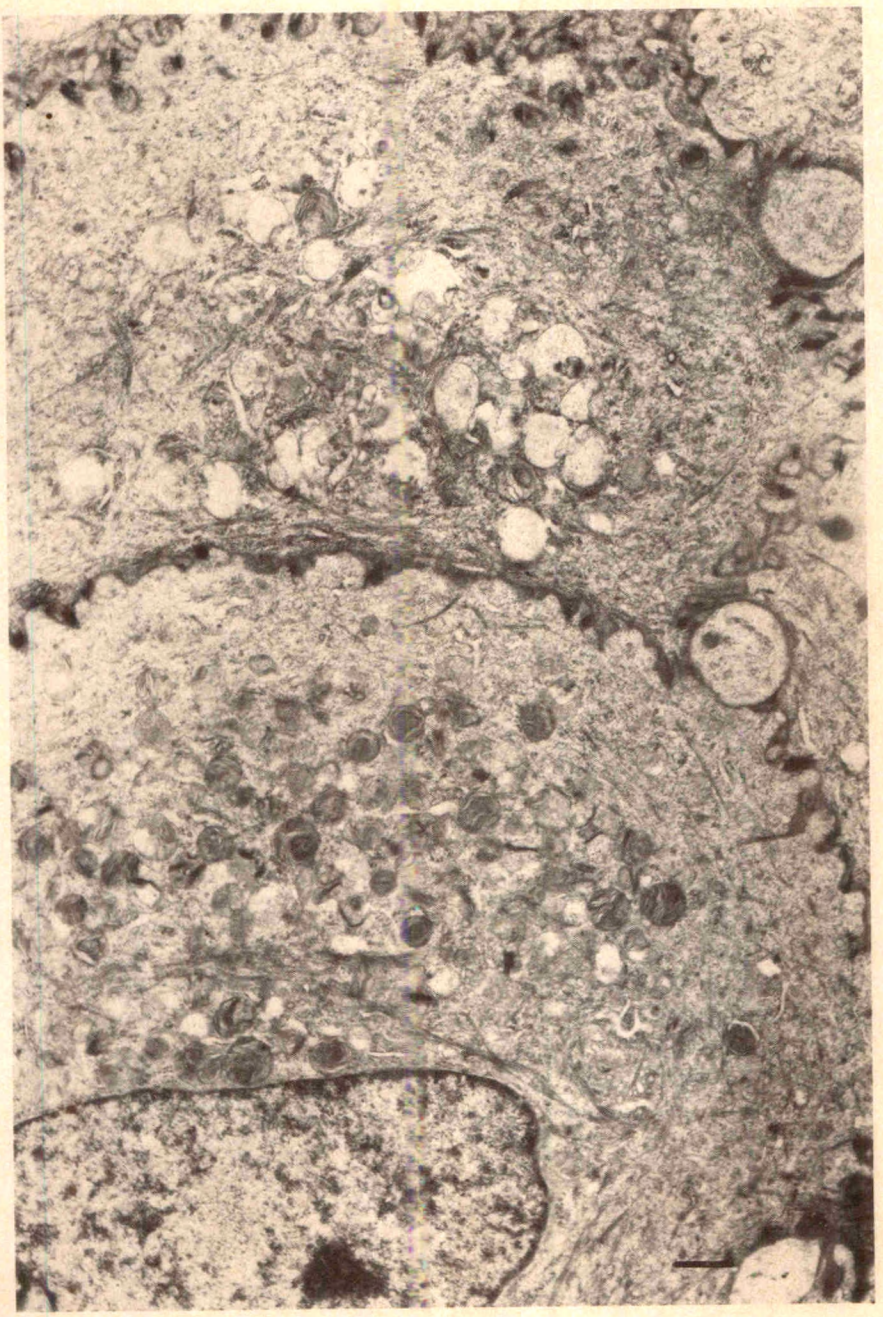


Fig. 5 (Newell, Matalon, and Meyer). Ultrastructure of the corneoscleral limbus. There are numerous inclusion bodies and many of the vacuoles are empty, others contain membranous lamellar material, and some contain both lamellar material and polymorphous material. Bar gauge = 1 μ (×8,000).

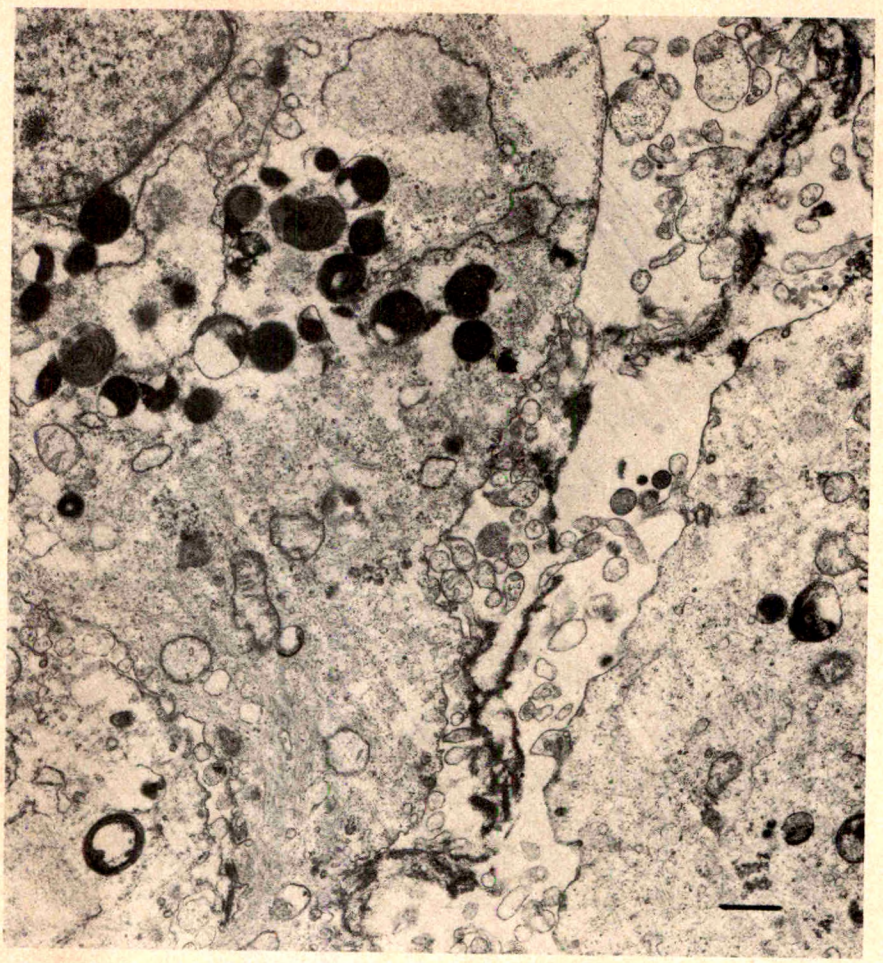


Fig. 6 (Newell, Matalon, and Meyer). Concentric membranous inclusion bodies and inclusion bodies with both membranes and polymorphous material (×78,500).

Tissue culture—The skin biopsy specimen was placed in modified Eagle's tissue culture medium, containing 10% calf serum and 10% fetal calf serum as described by Matalon and Dorfman.[6] Enzymatic studies were carried out as previously described. The following enzymes were assayed on the cultured fibroblasts; α- and β-galactosidase, α- and β-N-acetylhexosaminidase, α- and β-glucosidase, α-L-iduronidase, β-glucuronidase, arylsulfatases, A, B, and C, α- and β-mannosidase, and α- and β-fucosidase. Normal quantities were found. Metachromasia was not present.

Shreds of fibroblasts were removed from the culture and processed in the same manner as the conjunctival specimen. A pellet of fibroblasts secured from tissue culture, after centrifuging at approximately 7,000 rpm for 30 minutes, was also processed similarly, thick-sectioned (1 to 2 μ) and stained with toluidine blue, and thin-sectioned (400 to 600 nm) for electron microscopy.

Light microscopy of sections stained with toluidine blue indicated dark-staining particles of varying size that were found to be inclusion bodies (Fig. 7). These inclusion bodies were similar to those seen in the cornea and contained vacuoles, membranous materials, and

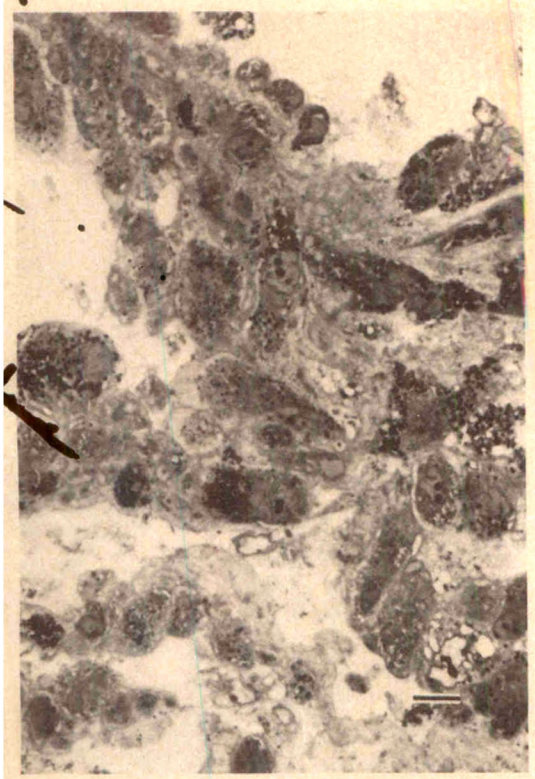


Fig. 7 (Newell, Matalon, and Meyer). Light microscopy of cells from tissue culture 1 to 2 μ thick. The darker dots outside of nuclei scattered through various cells are inclusion bodies. Bar gauge = 10 μ (toluidine blue, × 250).

polymorphous material. None of the material appeared to be extracellular and there appeared to be fewer vacuoles present; but polymorphous material was seen in nearly every cell.

Electron microscopy of the cultured fibroblasts indicated inclusions similar to those seen in the conjunctiva. These single-membrane-limited inclusion bodies contained membranous material (Figs. 8 and 9).

Based on the inclusion material in the conjunctival cells, the cultured fibroblasts similar to those seen in other storage disease, and the normal amount of all lysosomal hydrolases thus far studied, we concluded that this patient had a lysosomal storage disease. The enzymatic deficiency and chemical nature of the storage substance are unknown.

Discussion

Many different abnormalities are characterized by intracellular storage of various catabolic end products. Most abnormalities are inherited as autosomal recessive disorders, but Fabry's disease and type II mucopolysaccharidosis (Hunter's syndrome) are transmitted as X-chromosome-linked disorders.[7] Initially these were recognized because of their clinical similarity. In 1952, Brante[8] showed that the storage compound in Hurler's syndrome was a mucopolysaccharide. Since that time there have been enormous strides in the biochemical identification of the storage substance, the demonstration of the enzyme deficiency, and the identification of inclusion bodies containing normal products of cellular catabolism that cannot be further degraded because of a deficient enzyme.

The clinical abnormalities of the eye have been described in detail. Scheie, Hambrick, and Barness[9] demonstrated that the conjunctiva that appears clinically normal is similarly as involved as the cornea in those abnormalities.

Despite many studies there are patients who do not fit into the usual classification.[7] The deficiency of different isoenzymes results in related syndromes of variable severity and clinical signs. Additionally, some patients accumulate large quantities of compounds in the liver and brain not obviously related to the known enzyme deficiency, such as gangliosides in the brain of patients with Hurler's syndrome.

There have been few patients with mucolipidoses described (Table). These patients usually have a skeletal dysplasia, coarse features, mental retardation, neurologic abnormalities, no abnormal quantity of mucopolysaccharides in the urine, and no deficiency of the lysosomal enzymes customarily studied. Some degree of corneal clouding is present in many of



Fig. 8 (Newell, Matalon, and Meyer). Electron microscopy of cultured fibroblasts. There are scattered membranous inclusion bodies showing the concentric whorl-like material. Bar gauge = 1 μ (×8,000).

these patients. Tissues examined by using electron microscopy show intracellular accumulation of single-membrane-limited vacuoles containing either membranous lamellar bodies or polymorphous material. This material appears to be some type of storage substance. Culture of fibroblasts indicates inclusion bodies similar to those found in tissues.

The onset may occur at birth or as late

as age 7 years. The widespread storage of abnormal catabolic products in the tissues usually results in a slowly progressive disease with aggravation of clinical signs with increasing age. Death may occur relatively early in life. However, the two patients with mucolipidosis III had minimal clinical signs and were alive at ages 14 and 15 years. Our patient has survived to his 23rd year. In addition, rather than being progressively more severe, his corneal clouding seems less marked than it did in his early years. He also does not have the skeletal dysplasia and the coarse facies described in most other patients.

Patients with lysosomal storage disease constitute a unique clinical and biochemical resource. Our information concerning catabolism of the cell, the importance of lysosomes in body metabolism, and the biodegradation of metabolites in the cell has come about largely because of the study of these rare abnormalities.

Ophthalmologists who see patients with corneal clouding, with or without

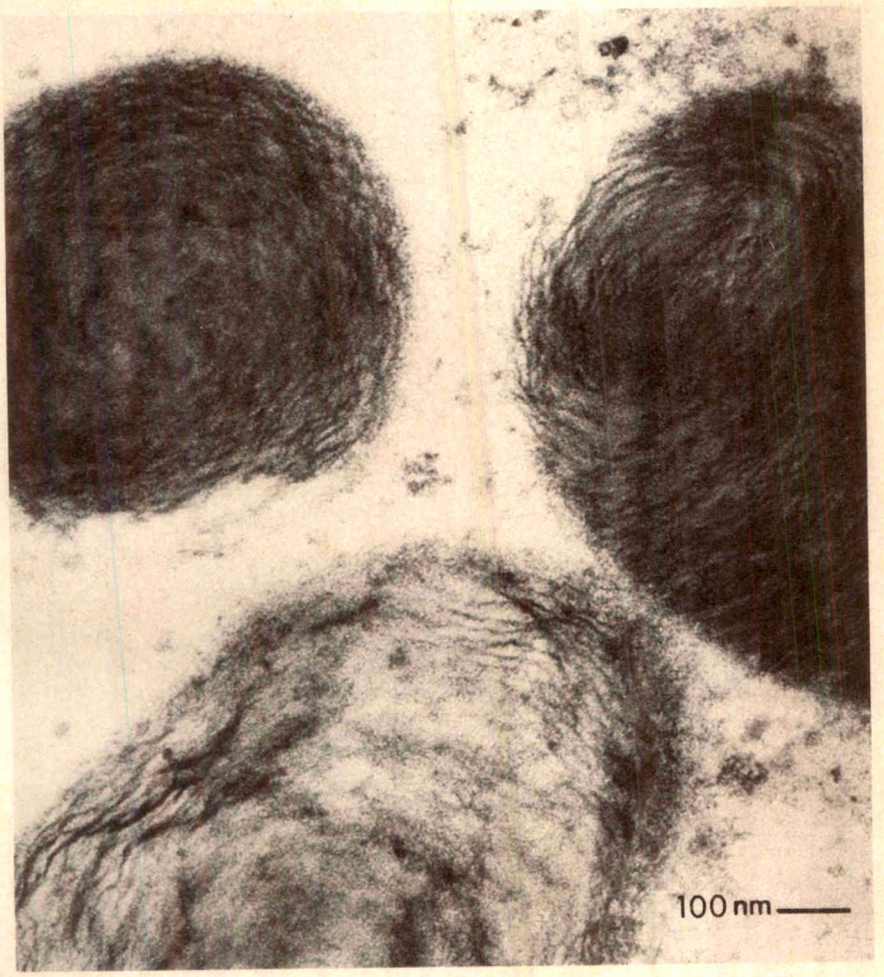


Fig. 9 (Newell, Matalon, and Meyer). Inclusion bodies from fibroblast culture. The inclusion body in the lower portion of the picture contains far fewer lamellae than those above (×95,760).

TABLE

CLINICAL AND DIAGNOSTIC FEATURES OF MUCOLIPIDOSIS

Disorder	Skeletal Dysplasia, Coarse Facies	Corneal Clouding	Intracellular Lesions: Membranous Lamellar Bodies	Intracellular Lesions: Single-Membrane Vacuoles	Enzyme Deficiency	Fibroblast Inclusion Bodies	Onset
Mucolipidosis I[3]	+ − + −	+ −	+	+	0	+	6 mos
Mucolipidosis II[10] (Inclusion-cell disease)	+ +	+ − 1 of 10 cases	+	+	+	+	Birth*
Mucolipidosis III[11] (Pseudo-Hurler polydystrophy)	+ +	+	+	+	NR†	+	7 yrs
Mucolipidosis IV[12] (Berman)	0 0	+	+	+	0	+	Birth‡
Present case	0 0	+	+	+	0	+	9 mos

*β-galactosidase of liver, 20 to 30% of normal; β-N-acetylhexosaminidase, 60 to 90% of normal; lysosomal hydrolases, 5 to 20% of normal.

†NR indicates not reported.

‡Findings at age 8 months.

retinal abnormalities, should cooperate in the studies that will ameliorate these disorders in the future. Laboratories working with these disorders are most happy to cooperate. Tissue culture permits cells to be frozen in liquid nitrogen so that the culture may be reactivated when new tests are available. It provides an immortality in which the cell line of a patient and the biochemical abnormality can be studied even though the patient is not available. Biochemical analysis of the tissue culture fluid and the cells combined with electron microscopy provides a wealth of information. There is not strict conformity, however, in the storage material found in the brain and liver at death, and biochemists should be provided with ice-cooled postmortem material as early as possible. The eyes of many of these patients have not been studied extensively in life by using modern tests of retinal function. Fewer eyes have been studied post morten with techniques combining light microscopy, histochemistry, and electron microscopy.

SUMMARY

A 23-year-old man had slow psychomotor development at 6 months of age and developed intermittent corneal clouding at about 18 months. He developed a truncal ataxia and hypotonia of the limbs combined with spasticity and active deep reflexes that did not progress. His skeleton and facies were normal. Between 1 and 13 years of age, he developed severe optic atrophy, absence of retinal blood vessels, and an extinguished electroretinogram. Biochemical analysis of cultured fibroblasts indicated no lysosomal hydrolase deficiency; cellular metachromasia was absent and there were no mucopolysaccharidoses. Ultrastructural studies in-

dicated single-membrane-limited vacuoles containing lamellated membranes and a polymorphous substance in tissue-cultured cells and conjunctiva.

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THE PAST 25 YEARS OF SURGERY

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It was with some trepidation, and yet some reason, that I selected the topic, "The past 25 years of retinal detachment surgery," to present to an audience in the city of San Francisco because in my review it became apparent to me that this region dominated retinal detachment surgery in the United States for at least two decades, extending from 1929 to 1949. The dominant person, of course, was Dohrmann Pischel who, with his father, was one of the first ophthalmologists in the United States to perform a successful, planned retinal detachment operation. This success was achieved shortly after Gonin's presentation to the International Congress in Amsterdam in 1929.[1]

During the preparation of this review there were at least two observations that have become apparent to me. One is that information is time consuming in its acquisition, publication, dissemination, and acceptance. The other is that history is seen through the eyes of the beholder and therefore reflects all his experiences and biases. Thus, unfortunately, truth is not defined by current popular opinion, but fortunately, truth will ultimately prevail.

Some examples of these two observations follow, and others will become self-evident throughout this presentation.

Retinal breaks in retinal detachment were observed as early as 1853 by Coccius,[2] shortly after the introduction of direct ophthalmoscopy by Helmholtz in 1850[3] and indirect ophthalmoscopy by Ruete in 1852,[4] yet it took Gonin from 1904 to 1919[5–8] to correlate the role of the break with the detachment itself, and it took him another decade before he could convince his colleagues that to cure a retinal detachment the surgeon must close the retinal breaks. Leber, in 1882,[9] put forth the concept that retinal breaks resulted from changes in the vitreous body that could be so subtle as to be unrecognizable by available examination techniques. He found little or no support for this theory until Dufour and Gonin revived it in 1906,[6] and until Gonin subsequently established the concept which persists to this day.

I will present here only the critical path of the past 25 years, from where we were to where we are, and will omit many side deviations which, in my opinion, have not and will not be on that critical path.

I have picked the past 25 years for two reasons. First, because I have been active in ophthalmology during this period and I have had the opportunity to work with or to communicate directly with the various people whom I shall mention and to discuss with them and their students the concepts and time relationships for the various developments. Second, the period begins shortly after World War II with what I consider are three major advances in the diagnosis and treatment of retinal diseases. These three advances have generated such great interest in vitreous-retinal diseases that, in this country alone, approximately 50 postresidency fellowships in the study of retinal disease are offered annually.

I can think of no effort in ophthalmology in the past quarter century that has paid so rich a dividend toward the prevention of blindness and the clinical care of patients.

The three advances I refer to are:

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1. The development of a new method for examination of the fundus by binocular stereoscopic indirect ophthalmoscopy combined with scleral depression. This was first presented by Charles Schepens[10] to the American Academy of Ophthalmology and Otolaryngology in 1946, and improved during the subsequent years when he worked in the Howe Laboratory, the Massachusetts Eye and Ear Infirmary, and the Retina Foundation. The instrument became commercially available in the early 1950s.

2. The origination of a scleral buckling procedure, as we currently conceive it, by Professor Ernst Custodis.[11] He began with animal experiments in 1947 and 1948, culminating with its first application to a human retinal detachment in 1949. His publication in 1953 reports 340 cases treated by this method.

3. The development of a light source and a delivery system capable of focusing high light energy onto the ocular fundus to create a controlled chorioretinal burn, photocoagulation. Experimental work, begun by Meyer-Schwickerath in 1946 in Hamburg and later in Bonn, culminated in a report to the International Congress in 1954[12] and the delivery by Zeiss of the first instruments to this country in 1958.

There has been much controversy over the originality and priority of these individual achievements, and one can easily become confused by the various statements in the literature. Such controversies may be of little consequence to the clinician and to the patient, but they are of great interest to the historian.

I have adopted the view that each of these men deserves tremendous credit for persistence in the development and refinement of his concepts, resulting in practical application to the patients.

While it is true that in 1861 Giraud-Teulon[13,14] described a binocular indirect ophthalmoscope and in 1900 Trantas[15] described scleral depression by use of his thumb to see the peripheral retina, for a variety of reasons, these techniques never gained acceptance.

Schepens, utilizing new instrumentation, developed this technique to such a high level that, once mastered, no more beautiful view of the fundus can be obtained and no substitute will be accepted.

Binocular indirect ophthalmoscopy gives an overall low-power view of the fundus which identifies those areas that need additional study by the high-power view of the slit lamp utilizing the Goldmann modifications of the Koeppe contact lens or the Hruby modification of the Lemoine-Valois preset corneal lens.

As Harrell Pierce has said, "You can take anything away from me except my binocular indirect ophthalmoscope and I still can carry out adequate retinal surgery."

While it is true that Jess,[16] in 1937, described in a two-page article the placement of a tampon of surgical sponge under Tenon's capsule to push the choroid and the retina together, he did not sew the sponge to the sclera. He made no further reports. Custodis, in his classic work,[11,17] reaffirmed Gonin's principle of closing the retinal breaks, but modified the technique so that the closure of the break was facilitated by suturing a foreign material onto the wall of the globe to cause an indentation of the sclera and choroid at the site of the break. He emphasized accurate localization of all of the breaks with indirect ophthalmoscopy (monocular); surface diathermy at the area of the breaks; suturing a "plombe," under tension, onto the ocular coats at the site of the break; this plombe (or "buckle" as we call it) must be wide and long enough to cover the entire retinal break, fluid drainage was not essential; and early ambulation of the patient was possible.

There can be little doubt that this original contribution by Custodis has proven to be the greatest advance in retinal sur-

gery since Gonin's publications.

While Czerny and Deutschmann, as well as others, focused sunlight onto a rabbit's fundus to produce a chorioretinal burn the persistence of Meyer-Schwickerath and the optical genius of Littman of the Zeiss Company (West Germany) resulted in the production of the first dependable instrument for the clinical application of photocoagulation.

Despite a flood of new xenon and laser instruments, the original Zeiss photocoagulator has stood the test of time, and is an essential piece of equipment in any retinal unit. Only time will tell whether the argon laser or some other unit will replace it, but future advances along this line will not detract from Meyer-Schwickerath's contribution. They will merely enhance it.

Having mentioned the three major advances that initiated and dominated this period of history, I will analyze in more detail the time sequence of some of the developments that have enhanced our knowledge of pathogenesis and have facilitated our examination and surgical techniques. I will then end this review with the consideration of the fourth major advance that has developed in the past decade and has only begun to approach its zenith: vitreous surgery.

Pathogenesis—Physicians, and especially surgeons, can achieve therapeutic success long before they have an understanding of the pathogenesis of the disease process. As I reviewed the tremendous improvement in our ability to cure retinal detachments that has occurred in the past quarter century, I was impressed with our lack of ability to advance our basic understanding of the initiating processes in this disease.

As a result of the work of Okun[18] and others,[19–21] we are much more conscious than before of the high incidence of asymptomatic retinal breaks unassociated with retinal detachments. As a result of the publications of Colyear and Pischel,[22,23] Byer,[24] and Davis,[25] we have a better understanding of the risk factors associated with retinal breaks, but we still do not understand why some cause retinal detachment and others seem to remain innocuous.

Likewise the high incidence of lattice degeneration in eye bank eyes, reported by Straatsma and Allen,[26] and confirmed by the meticulous, long-term clinical observations of Byer,[27] has not made life any easier for the retinal surgeon. In fact, it has made life all the more confusing when it comes to a judgment as to the appropriateness of prophylactic treatment.

Not all new knowledge enlightens. To paraphrase what Cogan once told me: A Harvard education is aimed at making you look carefully at both sides of a question, and this often results in confusion and indecision before a direct, and one would hope, correct course is taken.

It is apparent to any conscientious observer that we cannot prophylactically treat 6 to 10% of our population in order to prevent a disease that occurs in about 0.01% of our population, especially when the prophylactic treatment is neither innocuous nor inexpensive, and when our ability to treat the disease, once it occurs, is steadily improving.

On the basis of my own clinical practice, there can be little doubt but that far too many patients today are receiving prophylactic treatment. The problem remains, however, to delineate clearly many of the high-risk factors, such as superior horseshoe tears associated with vitreous hemorrhage; superior tears or lattice recognized before cataract extraction, especially if the first eye suffered a retinal detachment; a giant break in one eye of a patient with a strong family history of similar breaks, especially coming on after lens extraction; and the like.

Carefully controlled, randomized clinical trials, carried out in a collaborative effort, will be necessary to determine those patients at risk and the benefits, if any, from prophylactic treatment.

I do not want to leave the impression, however, that little or nothing has been accomplished during this period to advance our understanding of the pathophysiology of retinal detachment once it occurs. The experimental model, in the monkey, developed by Machemer and his co-workers,[28-37] has demonstrated an atrophy of the receptor outer segments, the collection of fluid in the intracellular spaces, and the loss of electrical response in the detached retina. All of these are rapidly reversed by the surgical reattachment of the retina. The radioisotope studies of Young[38] on regeneration of outer segments have also been repeated in the detached and reattached retina. Thus, we know that the outer segment of the neuroepithelium can regenerate—both rods and cones—and we suspect the pigment epithelium may act as a "pump" to keep fluid from under the retina, actually, to maintain a negative pressure to hold the retina in its normal place.

The role of the acid mucopolysaccharide material between the neuroepithelium and the pigment epithelium described by Zimmerman and Eastham[39] remains an enigma.

Examination—The importance of the examination with the binocular indirect ophthalmoscope and scleral depression cannot be overemphasized. Yet, in the United States, we were slow to use biomicroscopic slit-lamp examinations of the vitreous and ocular fundus, and especially the Goldmann three-mirror lens for examining the peripheral fundus.

In Europe, where monocular indirect ophthalmoscopy is common, there has been a great reluctance to accept binocular stereoscopic indirect ophthalmoscopy. On the other hand, Europe has led the way in the use of the stereoscopic biomicroscopic examination of the vitreous and fundus.

Figure 1 illustrates my own changing patterns of examination during the past 25 years. During my residency, I was trained exclusively in direct ophthalmoscopy, but it took only a few weeks in Boston, talking with the residents, to recognize my deficiencies and to learn of the new world that would be opened to me with the mastering of indirect ophthalmoscopy. The advantages have been clearly set forth elsewhere, and if you do not know them you have not mastered the technique.

As early as 1954 I used to tell the students that if they left their residency training without having learned indirect ophthalmoscopy, they were going out into practice a generation behind. I have no reason to change that statement.

It is important for the young people of today to realize that this was not an easy period in my life or in the lives of other young people who were trying to introduce this new technique to their institutions. Dr. Pierce at Wilmer was accused of making the retinal breaks with his scleral depressor; breaks that others could only see after careful detailed drawings had been made which led their direct view to the hole. I remember well, an elevated

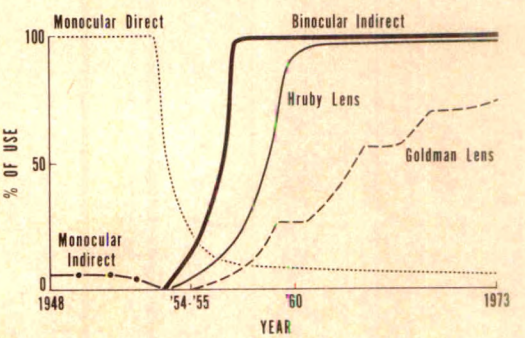


Fig. 1 (Norton). My changing patterns of opthalmoscopic examination.

flap at the ora serrata that was readily apparent with indirect ophthalmoscopy and scleral depression, but was interpreted by my teachers as an elevated mass. Not until I had surrounded the break with diathermy did they accept my view. I believe it is to McLean's credit that he placed immediate confidence in my integrity and observations and supported my efforts in the study of retinal disease.

With the increasing complexity of referral cases and our increasing ability to surgically attack the vitreous, the biomicroscopic examination utilizing the Hruby lens, and the Goldmann flat contact and three-mirror lens have been a natural and essential evolution.

Today we have come back to the best of two worlds: the panoramic overview with binocular indirect ophthalmoscopy with scleral depression, and the direct biomicroscopic magnified view of the vitreous and retina utilizing a variable slit, variable angle of observation, and focal illumination (Figs. 2 and 3).

Surgery—The surgical principles of Gonin, reemphasized and modified by Custodis, continue to be the framework upon which we build today. Apart from individual modifications, the critical path has been outlined above with the exception of two surgical procedures: the encircling buckle and vitreous surgery, which will be discussed below (Fig. 4).

The use of heat (diathermy, and the like), to set up the irritation of the chorioretinal tissue in the area of the breaks, has

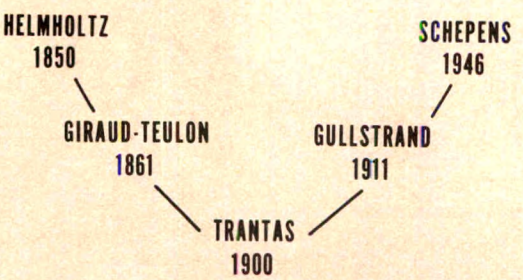


Fig. 2 (Norton). Critical path of ophthalmoscopy.

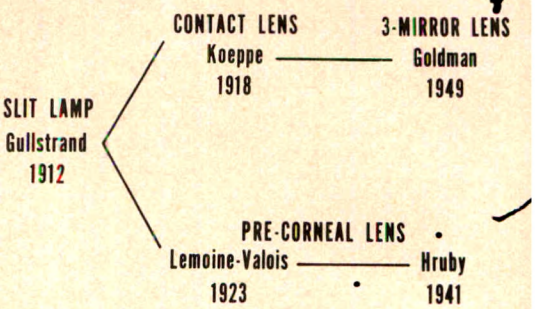


Fig. 3 (Norton). Critical path of biomicroscopy.

gradually been replaced by cold (cryotherapy), especially by those who prefer full-thickness scleral buckles, but I do not believe this has changed any of the principles of retinal surgery. I doubt if many detachments have been cured by the use of cold that would not have been cured by the appropriate use of diathermy, except in those cases of reoperation where the possible complications of scleral undermining increased the risks of surgery.

In no way is the above statement intended to detract from Lincoff who introduced the practical use of cryotherapy to retinal surgery.[40]

In 1933, Bietti[41] and Deutschmann[42] utilized cold to treat the area of the retinal breaks and Kelman and Cooper[43] published on the effects of cold on the pigment epithelium and retina, but Lincoff[44] deserves credit for having pursued this modality to its fruition in retinal surgery. While I believe diathermy will be used in the surgical treatment of a few selected types of retinal detachments, it will be replaced, if it has not already been, by cryotherapy.

While I am aware that in some institutions photocoagulation is used as the irritating modality, I do not believe that it belongs on the critical path of the surgical treatment of retinal detachments except in prophylactic treatment and some selected recurrences.

Twenty-five years ago full-thickness

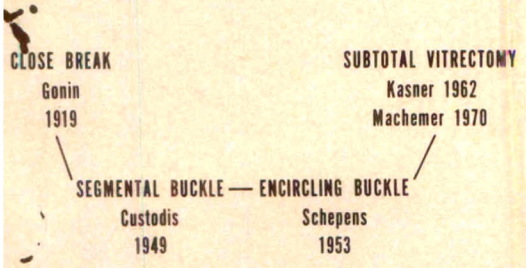


Fig. 4 (Norton). Critical path of retinal detachment surgery.

scleral resection, which had been introduced in 1903 by Müller,[45] revived and revised in 1933 by Lindner[46] and which continued to be advocated by Hruby,[47] was being replaced by lamellar scleral resection as advocated by Shapland.[48,49] This later modification was promptly accepted because it was considered to be as effective and considerably less dangerous than the full-thickness resection. Unfortunately, for the most part, those surgeons using these procedures intended to reduce the traction of the vitreous on the retina neglected consideration of Gonin's objective of closing the break. The scleral resection was carried out in a location convenient for the surgeon but without proper consideration of its relationship to the retinal break. Note how this procedure differed from Custodis's concept which was developing at this same time, but which had not yet been reported.

Interestingly, in the 1951 American Academy of Ophthalmology and Otolaryngology symposium on retinal surgery[50] scleral surgery was not discussed. Yet we know that it was common in Europe and Pischel and some of the members of that panel were using it in the United States.[51] Obviously there was disagreement within the panel as to its value.

When I joined the retina service in Boston as a fellow in July, 1954, having learned indirect ophthalmoscopy during the preceding three months working with Pierce at Wilmer, lamellar scleral resection, diathermy applied to the bed of the resection and the closure of the resection over a polyethylene tube, was a standard procedure. The resection was always located so that the buckle would be at the posterior edge of the most posterior break. The usual polyethylene tube used to make the buckle was approximately 1 or 2 mm in diameter. Thus, it was essential in larger breaks to connect the ends of the resection to the ora serrata, since anterior breaks or the anterior portion of the larger breaks, even though treated, could at times remain open and the anterior retina remain detached. The connections to the ora serrata delimited the detachment and in effect, when considered with the buckle, created a dam to isolate the anterior detachment. This procedure differed notably from that of Custodis, which demanded that the implant material used be wide enough to cover the entire break.

For historians, it may be important to know when the first localized implant into the sclera was performed by Schepens. My best estimate is that it was performed in late 1951 or 1952. This estimate is based on the publication of Smith and Pierce,[52] reporting all cases of retinal detachment operated on at the Massachusetts Eye and Ear Infirmary until July 1, 1951. This publication fails to mention either scleral surgery or the implantation of foreign material onto the sclera. This is in conflict with Schepen's[53] statement: "In 1957, I described my methods of scleral buckling based on eight years of experience, during which over 1,500 such operations were performed." Unfortunately, I am unable to resolve this conflict about dates. In any event, even if we assume that these ideas developed simultaneously and independently, Custodis adjusted the size and location of the scleral buckle (that is, the size of the implant material) to the size and location of the retinal break, while Schepens, at least initially, located the buckle so it would close the posterior aspect of the most posterior break.

Undoubtedly because of the increasingly difficult cases that were referred, in 1953 or 1954, Schepens originated the encircling buckle utilizing a polyethylene tube with an intraluminal suture.[54] I believe this was performed as a two-stage procedure initially: upper half and then lower half joined by an intraluminal suture. Despite the subsequent complications because of the suture material, the surgical "dead space," and the rigidity of the polyethylene tube, this must be considered a major advance in the management of complicated retinal detachments, especially those with severe vitreous traction; and it must appear as a milestone on the surgical critical path (Fig. 4).

Shortly after the introduction in the United States by Schepens of the polyethylene tube as the buckling material, it became apparent that wider implant material would be helpful to close the retinal breaks. Cuffs of polyethylene were used at first.

In 1958, Robb McDonald suggested the use of silicone rubber as a replacement for polyethylene. Beginning in 1960, the Boston group made available a wide variety of solid silicone bands and plates which almost immediately replaced polyethylene tubing.

This material was imbedded in undermined sclera, which was a surgical variation that replaced resection of the sclera in about 1957, and was suggested by Clark,[55] although it may have been originated by several people simultaneously.

Three advantages of silicone rubber implants then noted were: (1) the material was soft, pliable, and elastic; (2) the implant could be made large enough to cover the larger breaks; and (3) the dead space was eliminated.

Note how in 1960 we in the United States approximated the dicta Custodis had put into practice in 1949.

In 1963, silicone sponge was introduced by Dow Corning at the request of many investigators who, by now, had become aware of the work of Custodis, but were having problems with reactions to polyviol. Lincoff, utilizing this material as a replacement for polyviol and utilizing cryotherapy as a replacement for diathermy, popularized the Custodis procedure in its fullest sense—that is, even to the elimination of drainage of subretinal fluid.

Drainage of subretinal fluid—In Gonin's time, some subretinal fluid was automatically drained since his technique as described by Arruga was: "A Graefe knife is introduced at the point to be cauterized to a depth of 3 to 4 mm. . . . The point of thermocautery at red-white heat is introduced to a depth of 4 to 5 mm, left within the globe for two seconds. . . ."[56]

Because fluid drainage frequently left the eye soft, perforating pins were developed by Safar[57] to deliver penetrating diathermy without the loss of subretinal fluid, until the desired moment.

Twenty-five years ago, the use of Walker or Pischel pins for drainage of subretinal fluid was common in this country. I remember when I visited with Pischel in 1957, he used to jest about "seven come eleven," referring to the number of pins he would place, to be subsequently removed for the drainage of fluid. Others used penetrating diathermy for their drainage.

To the best of my knowledge, the use of a single sclerotomy site that could be closed by a suture and could be perforated for fluid drainage was developed by Schepens in 1947. This has remained the principal technique used for drainage of fluid by students of the Boston school to the present day. Some prefer to drain in the plane of the buckle and some posterior to the buckle, but in either case fluid drainage was an integral part of retinal surgery in the United States until 1958.

At the Ipswich Conference on the

"Importance of the Vitreous Body in Retina Surgery," Custodis made his first visit to the United States and shocked the participants by announcing that the drainage of subretinal fluid was not essential to the success of his technique. Many of the participants believed this to be a misunderstanding because of language difficulties, but on repeated questioning, Custodis insisted that he did not drain subretinal fluid.[58]

In 1960, Paul Wetzig and I observed Custodis's detachment surgery over an eight-day period and confirmed his statements. I remember seeing cases so highly detached over the buckle that I commented I would not sleep well if I had left a retinal break so elevated. Yet, the next day, the retina was flat and on the buckle.

In my mind, he had established beyond doubt that if the implant closed the break as it buckled in the coats of the globe, and if there was sufficient reaction around the break to seal it, the subretinal fluid could be "pumped out" by the pigment epithelium and the choroid.

Prior to Custodis's retirement, however, undoubtedly because of the referral of increasingly difficult cases, he drained fluid more often. In a recent communication from Custodis, he indicated that his student, Professor Linnen, now drains in approximately two thirds of his cases.

Presently, in my opinion, whether or not to drain subretinal fluid is a matter of judgment. One has to weigh the dangers of drainage against the risk of reoperation. This is a delicate balance which must be individualized to each patient.

Vitreous surgery—The concept of direct surgical intervention to remove vitreous opacities or to relieve vitroretinal traction has intrigued ophthalmic surgeons from at least the time of von Graefe.

Arruga describes Deutschmann's technique as follows: "He penetrated the ocular membranes behind the ora serrata with a double-edged knife, going from one side of the eye to the other . . . and sectioning the vitreous with swinging movements of the knife."[59] As Pischel observed: "This was a blind, if not blinding, procedure."

The variety of techniques of aspiration, implantation of vitreous substitutes, cutting of vitreous membranes by both the anterior and pars plana approach, have recently been reviewed in depth by Michels, Machemer, and Mueller-Jensen.[60]

In my judgment, the writings of Cibis[61] indicate that by 1965 he had already begun to conceptualize and to undertake vitreous surgery in a systematic manner. Unfortunately, his untimely death in April 1965 prevented him from completing his task, and from enjoying the rapid developments that have occurred during the past decade in the field of vitreous surgery.

In about 1961, Kasner,[62] in a planned operation, did a subtotal vitrectomy on a severely injured eye. He found that the eye tolerated the procedure and regained visual function. In 1966, he was probably the first to do a planned major subtotal vitrectomy for the removal of vitreous opacities, using the anterior approach.[63] Certainly his bold approach to anterior vitrectomy, when vitreous is lost at the time of cataract extraction, has been widely accepted and this has led him and others on to a more aggressive attitude toward vitreous removal.

Hal Freeman and his associates have approached vitreous membranes through the pars plana, utilizing indirect ophthalmoscopy, vitreous scissors, and even inflated balloons.

More recently, beginning in 1970, Machemer, Buettner, and Parel developed a series of instruments called the vitreous-infusion-suction-cutter (VISC), which enables the surgeon, utilizing the magnification of the operating microscope, to carry out subtotal vitrectomy via

the pars plana, leaving the anterior segment intact. With the addition of intraocular illumination supplied by a fiber optic system, even the finest vitreous strands are visible, and opaque vitreous can be removed. Proliferations spreading out on the back of the detached vitreous can be cut and bleeding vessels coagulated. Vitreous membranes spanning the vitreous cavity, exerting traction on the retina, and causing a detachment, can be readily removed and, in selected cases, membranes can be removed from the immediate surface of the retina.

New instruments have already been developed with the hope of improving on these techniques, and I am certain that the dawn has just broken on this type of surgery.

SUMMARY

The past 25 years have seen an explosion in interest and progress in the diagnosis and treatment of vitreoretinal diseases, especially retinal detachments. This progress has paid high dividends in the prevention of blindness and the clinical care of patients.

The major advances during this period are the development of a binocular stereoscopic indirect ophthalmoscope combined with scleral depression, the introduction of a scleral buckling procedure to close retinal breaks, the development of instruments capable of producing controlled focal irritation in the ocular fundus, and the advent of direct surgical removal of the vitreous.

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THE USE OF DIAGRAMS TO RECORD CHANGES IN GLAUCOMATOUS DISKS

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The demonstration of increasing cupping of the optic disk in glaucoma is as important as increasing field loss in documenting progression of glaucomatous damage. The size and contour of a particular disk must be accurately recorded. Good quality stereoscopic photographs of the disks that are compared at regular intervals provide a reliable method for such assessment. On the other hand, the difficulty and time involved in dilating the pupil to permit photography, and the variable quality of the photographs obtained, decrease the practicality of disk photography in a busy ophthalmologic practice. Volume changes in the cup by stereogrammetry may be an even more sensitive way of detecting small degrees of progressive cup enlargement, but such sophisticated equipment will probably never be available to the practicing physician. Disk diagramming remains a quick and efficient method of charting disk changes. Pickard[1] described such a method more than 50 years ago. The adaptation presented here has proven useful in clinical practice.[2]

METHOD

There are two important factors for grading optic cups, color and contour, that should be documented. The vascular supply to the neurons produces the familiar pinkness of the nerve fibers of the optic disk in contrast to the pallor of the lamina cribrosa. This pallor-to-pinkness ratio has been used to establish the cup/disk ratio by color. Contour can also be used by considering the beginning of the cup to be that point where the nerve fibers angle posteriorly away from the retinal surface. Either or both of these factors can change, and a careful initial diagram can aid greatly in therapeutic decisions. Minor changes in disk cupping may not be noticed, but major changes become obvious.

Reliability of the numerical assessment of cup/disk ratio—The usefulness of the cup/disk ratio depends on the clinician's ability to make a reliable numerical assessment of the actual size relationship between the cup and the disk. To test this ability, 16 subjects (eight ophthalmology residents and eight ophthalmology staff members) viewed 48 Kodachrome slides depicting two circles of known diameter (Fig. 1, left). A larger outer circle that represented the outer edge of the optic disk remained constant. A variable-sized inner circle represented the optic cup with the ratio of its diameter in relation to the outer circle ranging from 0.1 to 0.9. Twenty-seven slides presented ratios of 0.1, 0.2, and the like, where a precise estimation to the nearest 0.1 was possible. Twenty-one slides presented ratios of 0.15, 0.25, and the like, in which a precise estimation to the nearest 0.1 was impossible. Observers were instructed to estimate the ratios on each slide to the nearest 0.1, so they were forced to round off and err by at least 0.05 in 21 of the 48 slides. To approximate the clinical situation the inner circle was sometimes placed eccentrically (Fig. 1, right). Each slide was presented for 15 seconds, and the observers recorded their estimates of the ratio of

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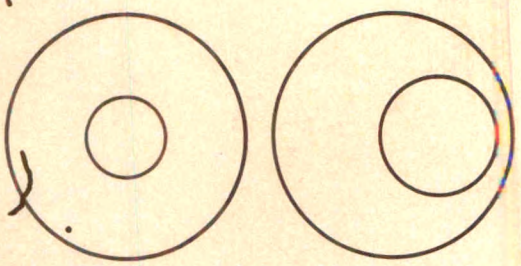


Fig. 1 (Shaffer and associates). Left, Two circles of known diameter. Right, The inner circle is placed eccentrically.

the diameter of the inner to the outer circle to the nearest tenth.

RESULTS

In those slides in which a precise estimation was possible the group misjudged the ratio more than eight in 27 times, a 33% rate of error. The resident and the staff groups performed comparably. Ninety-five percent of the errors were within + or − 0.1. There were no miscalculations greater than 0.2. The majority of errors (78%) were underestimates. There was a tendency for individual subjects to be consistently either over- or underestimators. There were more errors when the inner circle was eccentrically placed. Forty-six percent of the errors occurred between ratios of 0.4 to 0.6, 23% between 0.1 to 0.3, and 31% between 0.7 to 0.9.

The subjects were given no feedback concerning the correctness of their estimates during the test; estimating ability could be materially improved by training. Indeed, many observers reported that taking the test enhanced their skill at clinical cup/disk estimates.

In unambiguous line drawings, observers usually estimated the ratios of the diameters of two circles to an accuracy of + or − 0.1. The ambiguities of cup and disk border discrimination in the clinical setting amplified the problems in estimation of the ratio. It would seem necessary to have a change of at least 0.2 disk diameters to be confident that a real change had taken place.

DISCUSSION

Diagramming method—Figure 2 shows the chart of the two disks used for the diagram. The two circles representing the outside diameter of each disk are divided into squares of 0.2 disk diameters each. The cup/disk ratio is then expressed in tenths of a disk diameter. The chart is reproduced in the patient's history by a rubber stamp.

At the periphery of the disk the inner layer of the neurons is at the level of the retina. The center of the disk where the blood vessels emerge is the deepest part of the optic cup. It looks pale due to the whiteness of the lamina cribrosa and the glial tissue. The nerve fibers come through the lamina carrying their capillary blood supply with them. As this layer of fibers becomes thicker their blood supply makes the nerves look pink. In diagramming the disk an inner circle is drawn representing one's best estimate of the interface between neurons and the lamina cribrosa as identified by the pinkness-to-pallor ratio. A solid line to the circle indicates a vertical or undermined edge of the cup; dashed lines on the inner circle show a sloping edge. Most observers compare the area of paleness to the diameter of the disk, calling it the cup/disk ratio, expressed in tenths.

The second important factor is the contour of the disk. There is considerable saucerization of a disk without change in the pinkness-to-pallor ratio in some cases. A second peripheral circle inside the disk margin is used to show where the nerve fibers reach the approximate level of the surrounding retina. The steepness of the slope is shown by several radial lines between the inner and outer circles (Fig. 3). No outer line is needed if the central cup is small (Fig. 4). The dashed lines show there is a slope to the edge of the

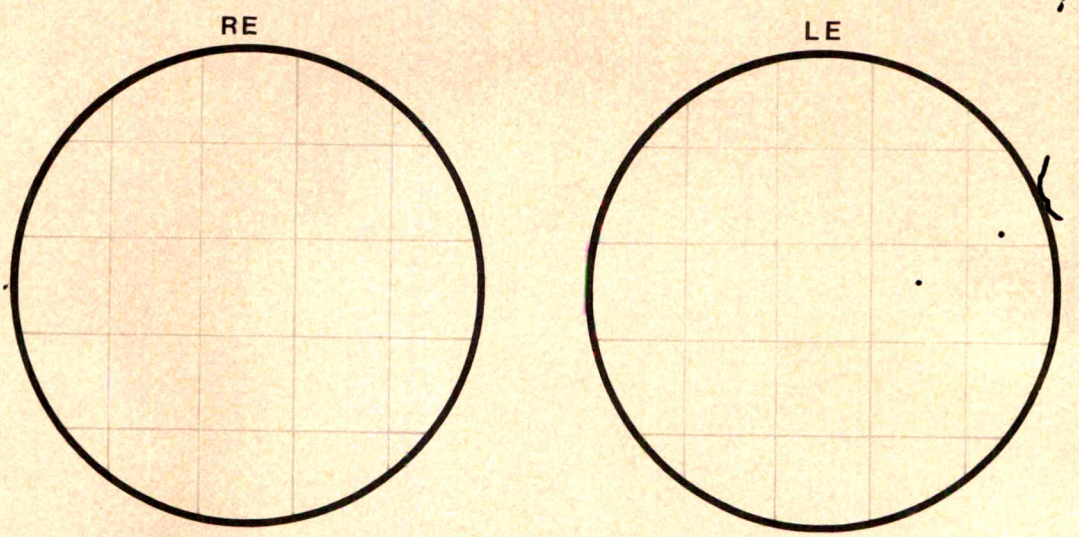
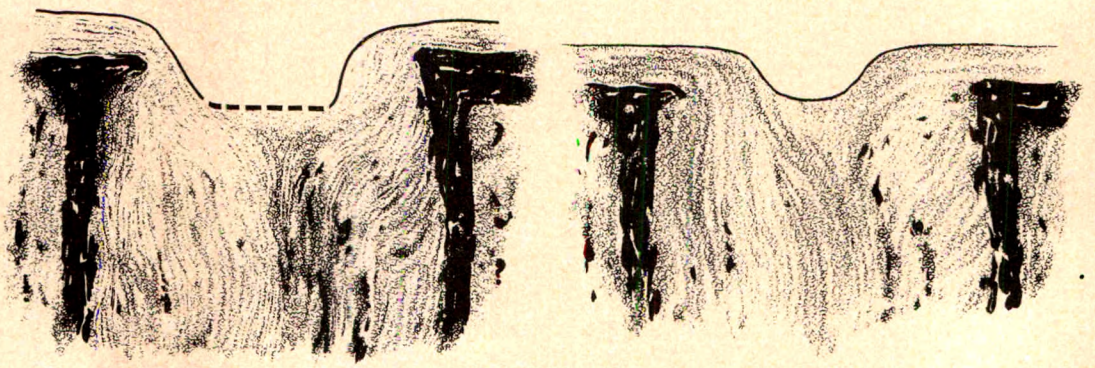


Fig. 2 (Shaffer and associates). In this disk diagramming chart the cup/disk ratio is expressed in tenths of a disk diameter.



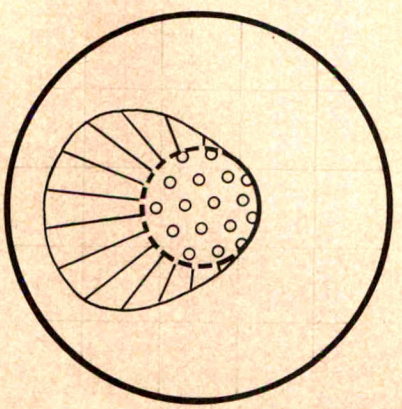


Fig. 3 (Shaffer and associates). This optic disk has a 0.3 cup/disk ratio. The lamina cribrosa is slightly exposed, as shown by the small circles.

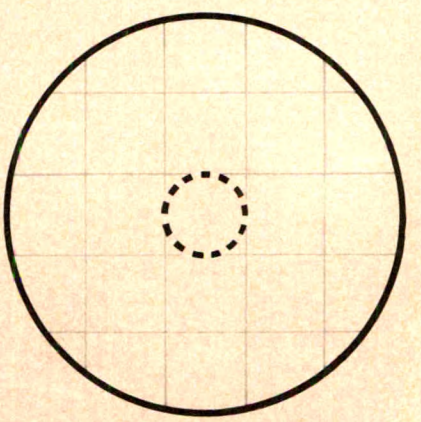


Fig. 4 (Shaffer and associates). In this normal disk, the cup/disk ratio is 0.2.



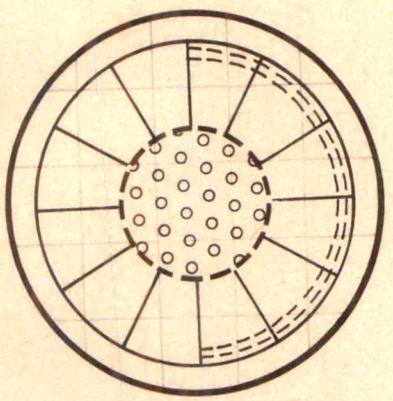


Fig. 5 (Shaffer and associates). The short concentric lines in this disk with a 0.4 cup/disk ratio indicate a slope that steepens abruptly.

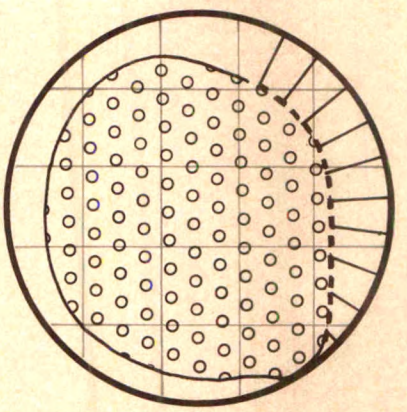


Fig. 6 (Shaffer and associates). A typical glaucomatous cup is shown with a cup/disk ratio of 0.7 horizontally, and 0.9 vertically. Note the loss of nerve fibers of the lower temporal rim.

cup but most of the disk surface is at the level of the retina.

Some refinements to the basic diagram are helpful. The slope of nerve fibers from the lamina to the retinal level may not be uniform. Areas of increased slope are shown by adding small concentric dashes to the radial lines (Fig. 5). If the lamina cribrosa is exposed, its sieve-like anatomy forms the "laminar dot sign" described by Read and Spaeth[3] and is diagrammed by tiny circles or cross-hatching (Figs. 3 and 5). Enlargement of the area of laminar dots in subsequent examinations indicates a loss of neural tissue in front of the lamina.

Examples—A normal disk is diagrammed in Figure 4. It has a small cup with sloping borders that promptly reach the level of the surrounding retina. No radial lines are needed. The cup/disk ratio is 0.2. The small central area of pallor is made up of glial tissue and the lamina cribrosa is not exposed.

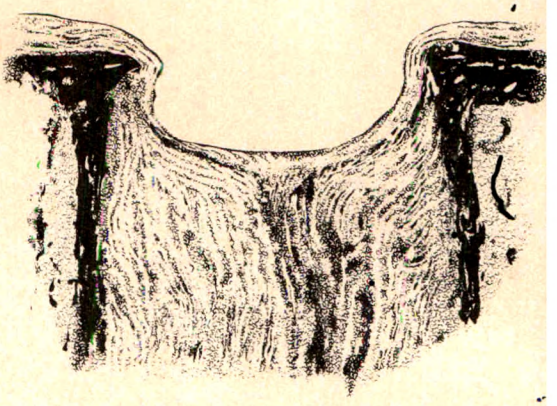
The optic disk in Figure 3 has a 0.3 cup/disk ratio that is slightly deeper, exposing the lamina cribrosa, shown by the small circles. The nerve fibers begin at the inner dotted circle and rise toward the retinal surface near the periphery of the disk as shown by the straight radial lines. On the other side there is a steep slope as shown by the solid line.

In Figure 5, there is a 0.4 cup/disk ratio with an upward slope to the retinal level near the edge of the disk. On one side, the slope steepens abruptly as shown by the short concentric lines. The lamina cribrosa is exposed as shown by the circles.

Figure 6 shows the contour of a typical glaucomatous cup. The color contrast shows a cup/disk ratio of 0.7 (horizontal) × 0.9 (vertical) with an extension to the lower temporal rim, exposing large areas of the lamina cribrosa. The loss of nerve tissue to the edge of the disk is almost invariably associated with an arcuate field defect. One half of the cup is steep-walled as shown by the solid line. The other half of the cup has a slope that reaches the retinal level near the periphery of the disk.

In Figure 7, there is a severely cupped disk with steep edges to the cup of more than 0.8 disk diameters. The lamina cribrosa is exposed. Since the nerve fibers at the disk margin may be intact, one could not predict the presence of a field defect. A patient with such a disk should have careful perimetric studies and must remain under observation. Asymmetry of cupping is a good indication of glaucomatous damage, and is often easily seen in bilateral disk diagrams.

In clinical practice this method of disk diagramming is an easy, quick, and effective method of recording the appearance of the disk. Future changes can be compared readily to the initial diagrams. Often, changes can be seen before field changes occur. Unless the disk is easily visible, dilation of the pupil is advisable every year. If there is any doubt of the contour, or if the perimetric findings are not consistent with the visible appearance of the disk, the examination should include binocular evaluation of the disk through a dilated pupil using a fundus contact lens and the slit-lamp microscope.



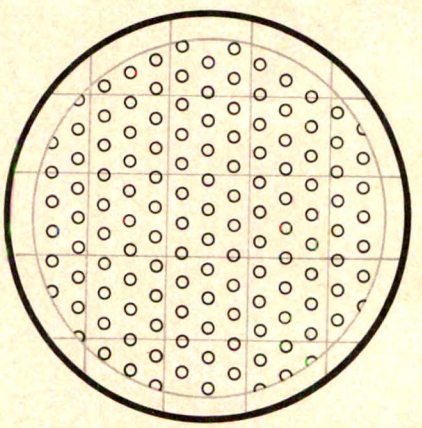


Fig. 7 (Shaffer and associates). A cup/disk ratio of 0.8 is shown with a uniform rim of nerve tissue.

Summary

We devised a quick and effective method of diagramming the appearance of the optic disk by using two circles divided into squares of 0.2 disk diameters each. If stereoscopic color photographs of the disks are unavailable, diagramming is a useful substitute.

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OPTIC NERVE EXTENSION OF INTRAOCULAR NEOPLASMS

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The dispersion of viable neoplastic cells from the surface of a primary intraocular neoplasm is a well-known phenomenon best exemplified by retinoblastomas. Such tumors, particularly those with an endophytic growth pattern, tend to shed clusters of cells into the vitreous cavity where they spread to other intraocular sites, and adhere, multiply, and invade tissues producing secondary neoplasms. The optic nerve head and nerve are often invaded in this manner. Because of this, clinicians have transected the optic nerve as posteriorly as possible at enucleation to ensure complete removal of the tumor.

Some types of uveal melanomas behave in a fashion similar to retinoblastomas. Seeding of viable melanotic tumor cells may occur into the vitreous body from the surface of melanomas in the ciliary body and from choroidal melanomas that extend through the retina. Similarly, melanomas in the iris may shed cells into the aqueous body. Cells from these types of melanomas and from endophytic retinoblastomas tend to invade the optic nerve head and optic nerve; angle-closure glaucoma can enhance this invasion.

MATERIAL

Eight choroidal melanomas and two melanomas of the iris and ciliary body were studied. One of the eyes containing melanomas of the iris and ciliary body has been reported previously[1] (Case 1, Table). At the time of enucleation, this eye was glaucomatous and there was no light perception. Upon gross examination of the enucleated specimen, the distal end of the optic nerve at the site of surgical transection appeared unremarkable (Fig. 1, top). However, on cross section of the optic nerve immediately behind the sclera the nerve appeared jet black (Fig. 1, center). A second cross section 3 mm posterior to the first cut also appeared black (Fig. 1, bottom). On microscopic section, the eye contained a necrotic diffuse malignant melanoma of the iris and ciliary body (Fig. 2, top) which occluded the chamber angle. Tumor cells were dispersed throughout the posterior segment of the globe. The retina was invaded by tumor cells in many areas (Fig. 2, bottom) as was the optic nerve head and optic nerve. The choroid was free of tumor. The patient died of metastatic melanoma one year after enucleation. There was no clinical evidence of orbital recurrence of the tumor during this interval.

In Case 2, the melanoma in the necrotic iris and ciliary body had caused secondary angle-closure glaucoma and had spread posteriorly to invade the optic nerve head, optic nerve, and retina in a diffuse fashion. As with Case 1, the patient was unable to perceive light with this eye before enucleation. No evidence of local recurrence or metastases was observed in the 15-month period of follow-up.

Necrotic choroidal melanomas may extend through Bruch's membrane and the overlying retina into the vitreous body where they may disperse viable tumor cells that gain access to and invade the optic nerve head and nerve (Fig. 3). Each

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TABLE

PATIENT DATA*

Case No., Age, yrs	Cell Type	Extent Of Optic Nerve Extension	Orbital Recurrence	Follow-Up
1, 56	Necrotic, diffuse	5 mm	–	Died 1 yr after enucleation with metastases
2, 76	Necrotic, diffuse	4 mm	–	Living and well 15 mos after enucleation
3, 72	Epithelioid with necrotic areas	2 mm to site of surgical transection	+	Died 9 mos after enucleation with metastases
4, 62	Epithelioid with necrotic areas	5 mm to site of surgical transection	+	Died 2 yr after enucleation with metastases
5, 67	Epithelioid with necrosis	To orbital apex	–	Died 13 mos after enucleation with intracranial extension
6, 70	Necrotic, diffuse	Minimal-scattered tumor cells in retrocranial optic nerve	–	Died 11 yrs after enucleation of cardiac causes
7, 70	Mixed	3 mm, also had extrascleral extension	+	Died 4 yrs after enucleation with intracranial extension
8, 59	Necrotic	2 mm to site of surgical transection	+	Developed metastasis 8 mos after enucleation
9, 89	Necrotic	Minimal with scattered tumor cells in retrolaminar optic nerve	–	Living and well 13 mos after enucleation
10, 70	Necrotic	1 mm	–	Living and well 14 mos after enucleation

*All patients had glaucoma and no light perception.

patient had glaucoma and there was loss of light perception. In five of the eight cases, the surgeon transected the optic nerve through the site of tumor extension (Fig. 4) and, in four of these five, orbital recurrences were clinically detected in four to 14 months. Orbital recurrences were not observed in the other four patients.

The degree of optic nerve invasion in these patients varied, ranging from a few collections of tumor cells lying in the

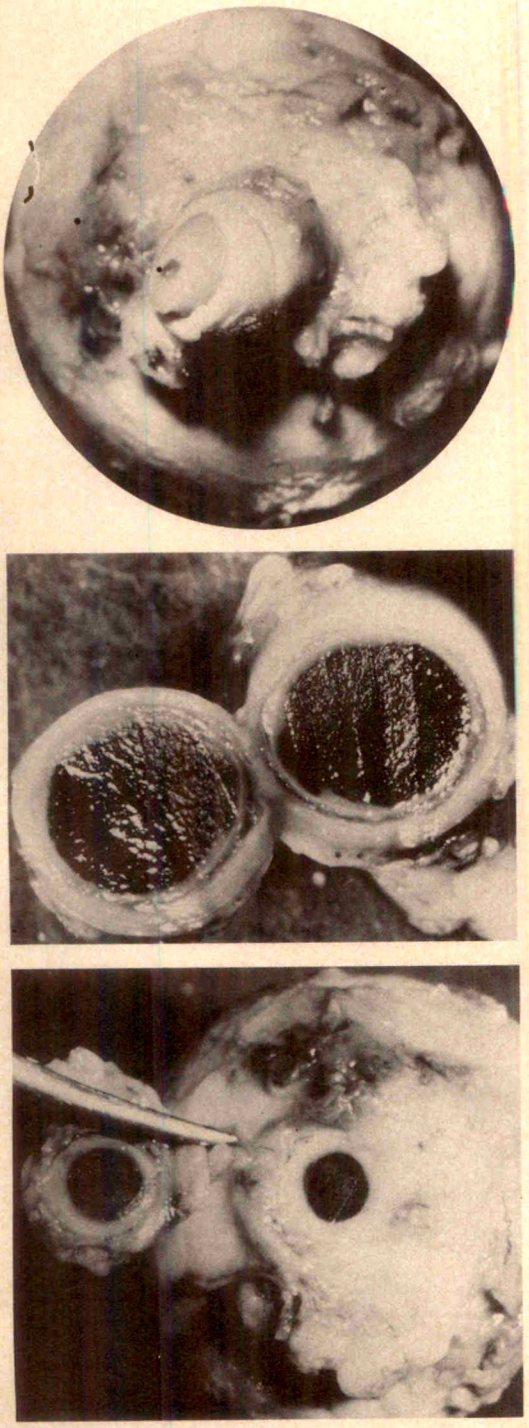


Fig. 1 (Spencer). Case 1. Top, Posterior view of enucleated eye showing normal appearance of optic nerve at site of surgical transection. Center, Transected nerve at level of sclera showing tumor. Bottom, Transected optic nerve 3 mm behind sclera showing tumor.

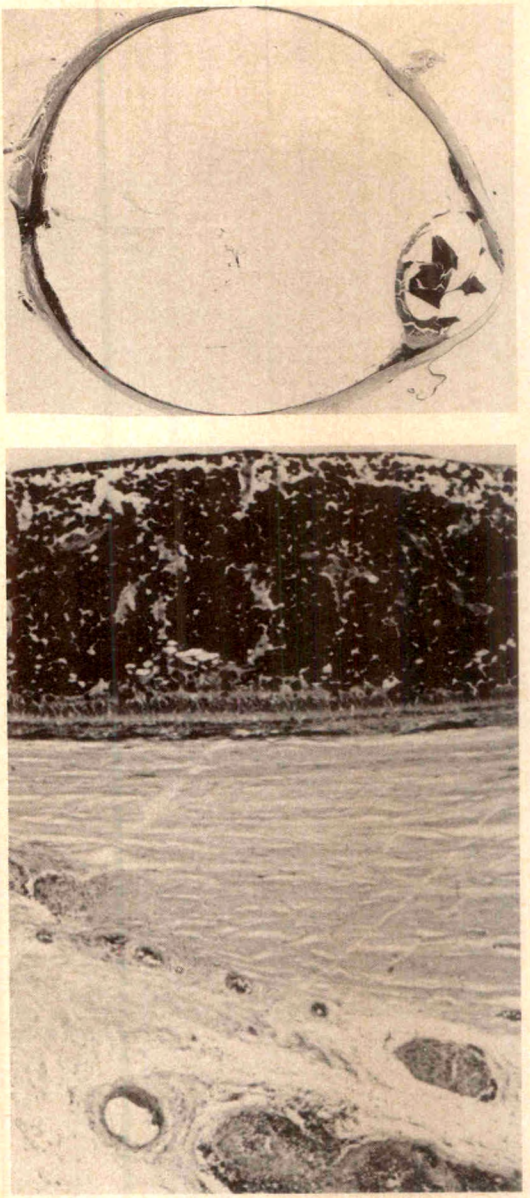


Fig. 2 (Spencer). Case 1. Top, Diffuse melanoma arising in the iris and ciliary body and extending posteriorly to involve the retina and optic nerve head. Bottom, Retinal invasion by melanoma. The choroid is not involved (hematoxylin and eosin, ×1.0).

anterior portion of the nerve (Fig. 5) to invasion of the entire nerve. According to Frederick C. Blodi (personal communication Jan. 9, 1973), the optic nerve in one patient (Case 5) was invaded to the orbital

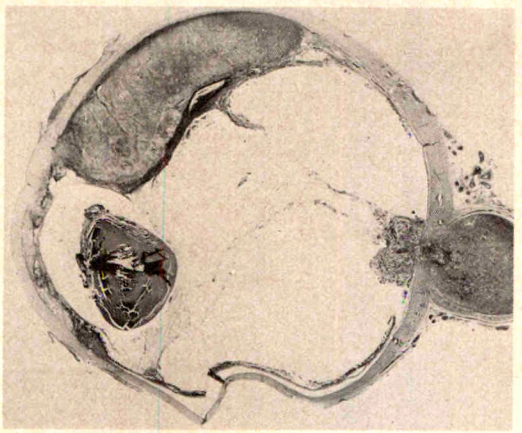


Fig. 3 (Spencer). Case 3. Choroidal and ciliary body melanoma extends into the vitreous body and spreads to optic nerve.

apex and probably to the chiasm. The patient, a 67-year-old white man, had his blind left eye enucleated in February 1967. The eye had angle-closure glaucoma with rubeosis. A large necrotic choroidal melanoma that had invaded the optic nerve to the severed end was found. In July 1967, an exenteration of the orbital contents was performed and the optic nerve was invaded by melanoma to the orbital apex. The patient was treated with intravenously administered thiotepa. In August, vision in the right eye began to dim and by November there was a hemianopic visual field defect in the right eye, suggesting chiasmal invasion. The patient died of the complications of intracranial melanoma in March 1968. An autopsy to confirm the chiasmal invasion was not done.

All of the tumors including the melanomas of the iris and ciliary body contained many epithelioid-type cells and most showed areas of necrosis often accompanied by hemorrhage. In the 1951 report by Wilder and Paul[2] of 2,535 cases of malignant melanoma of the choroid and ciliary body, 16 necrotic melanomas had tumor extensions along the optic nerve to the line of optic nerve excision. All 16 patients died of metastases. No mention was made of orbital recurrences.

Discussion

Several factors appear to be necessary for optic nerve invasion by intraocular melanomas. Viable melanoma cells must be able to gain access to the optic nerve head. They may be shed either from the surface of noncohesive tumors of the iris

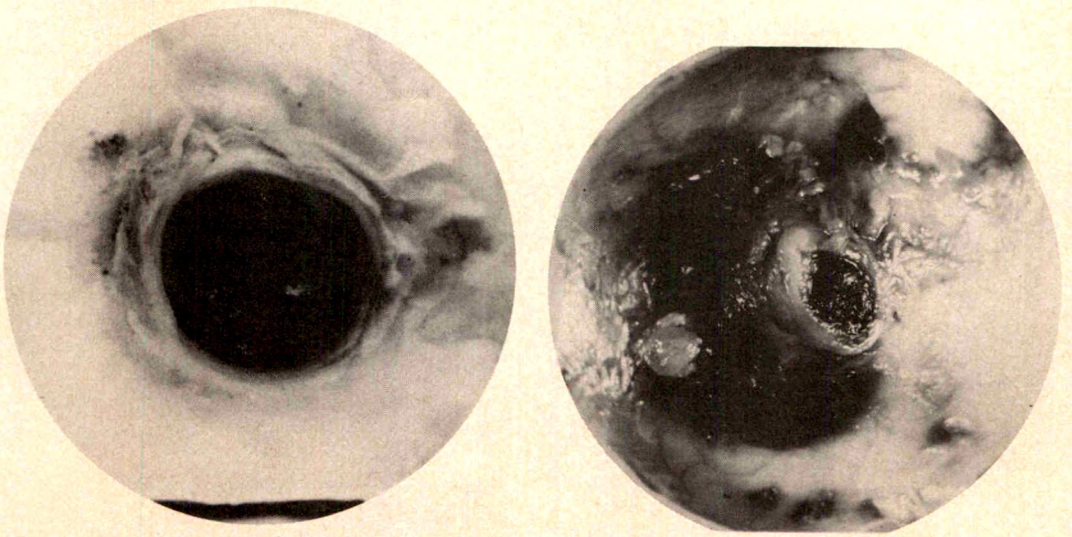


Fig. 4 (Spencer). Left, Case 3. Site of surgical transection of optic nerve showing tumor. Right, Case 4. Site of surgical transection of optic nerve showing tumor.



Fig. 5 (Spencer). Case 6. Scattered tumor cells (black spots) lie in the postlaminar portion of the optic nerve. The prelaminar nerve is partially necrotic (hematoxylin and eosin, ×10).

or from melanomas of the choroid or ciliary body that have broken through into the vitreous cavity. This type of shedding appears to be associated with more malignant melanoma cell types particularly with those in which necrosis or hemorrhage has occurred. In general, peripapillary melanomas do not invade the optic nerve in the same manner. When they do, these tumors extend past the end of Bruch's membrane and into the optic nerve head to produce compression and distortion of the nerve head without appreciable invasion of the retrolaminar portions of the nerve. Extraocular extension of these tumors usually occurs via the intrascleral channels of the short posterior ciliary vessels and nerve than it does by the nerve itself.

The tumor cells spread to the optic nerve from anterior segment tumors either around or through the vitreous body. Direct continuity by progression of tumor cell growth along the inner surface of the retina is unlikely. A parallel situation in a nonneoplastic ocular condition occurs in phakolytic glaucoma where macrophages containing lens protein are often observed histologically along the inner surface of the posterior retina and the optic nerve head.

In all of these cases, the normal anterior segment channels for aqueous outflow were blocked by peripheral anterior synechiae or tumor cells, and limited secondary posterior pathways probably developed. A portion of this posterior aqueous flow may have transported viable tumor cells through the vitreous cavity that appeared histologically abnormal in all cases.

Posterior dispersion of viable iris tumor cells shed into the aqueous tumor does not seem to occur in the absence of glaucoma. I observed cases of this type in which secondary inferior iris and angle tumors developed in the absence of glaucoma with no clinical or histologic evidence of posterior dispersion of tumor cells.

Increased intraocular pressure may also have augmented the initiation of neoplastic invasion of the optic nerve head in these cases. During extended periods of increased intraocular pressure, the tissues of the optic nerve head undergo swelling and become edematous. This may be accompanied by loss of nerve conduction. In all of these cases, there was marked increased intraocular pressure, and it is possible that the associated ischemia and edema of the optic nerve head interrupted the integrity of the tissues and enhanced the initiation of neoplastic invasion. Experimental evidence suggests that cavernous degeneration of the optic nerve may be related to increased intraocular pressure.[3] In this condition, hyaluronic acid presumably derived from the vitreous cavity is present in cavernous spaces in the optic nerve head and retrolaminar optic nerve where it replaced axons that underwent dissolution. A similar mecha-

nism may be operative in these cases. Hyaluronidase-sensitive acid mucopolysaccharide positive material was present in the retrolaminar portions of the optic nerve in the three cases in which the stain was performed. Its origin is uncertain, however, since similar material may have been produced by the melanoma cells residing in the optic nerve.

In order to gain a better insight into the possible role of glaucomatous enhancement of optic nerve head invasion, I reviewed 38 cases of endophytic retinoblastomas with optic nerve head invasion. Twenty-nine patients had rubeosis and angle-closure glaucoma while nine had no histologic evidence or history of glaucoma. It appears that endophytic retinoblastoma can invade the optic nerve head in the absence of glaucoma, but the invasion appears to be enhanced by the presence of increased intraocular pressure.

Complete absence of light perception is a distinctly unusual phenomenon in most cases of intraocular melanoma, yet it developed in each of the cases with optic nerve invasion. Absence of light perception is difficult to assess in children with retinoblastomas, but in those old enough to respond it would be helpful to determine whether or not light perception is present in assessing the presence or absence of optic nerve invasion.

The sequence of events that occurred in the optic nerve head of these cases is not known. The nerve conduction loss may have been initiated by the increased intraocular pressure accompanying angle-closure glaucoma. Development of cavernous degeneration with concurrent neoplastic invasion and permanent interruption of axonal conduction may then have occurred. The presence of hyaluronidase-sensitive acid mucopolysaccharide in the retrolaminar portions of three early melanoma cases suggests this likelihood. Conversely, the optic nerve head invasion may be unrelated to the glaucoma, but solely due to the ability of dispersed viable melanoma or retinoblastoma cells to adhere to and invade these tissues. The necrosis of the nerve induced by neoplastic proliferation may then have permitted the hyaluronic acid to migrate posteriorly.

A long piece of optic nerve should be excised at enucleation of an eye suspected of harboring a necrotic malignant melanoma, especially if there is secondary glaucoma and absence of light perception. Observation of the cut surface of the optic nerve in the operating room may reveal evidence of incomplete excision and signify the need for excision of more posterior portions of the nerve and possibly of the orbital contents. This procedure may reduce the incidence of orbital recurrence of the tumor. I do not know whether the prognosis for life is materially affected by complete local excision of the tumor. The poor prognosis in these patients appears to be the result of several combined features including the presence of epithelioid cell and necrotic types of melanoma and the large size of the tumors. The retrospective study of endophytic retinoblastoma cases suggests that there is enhanced invasion of the optic nerve head by retinoblastoma cells in eyes with angle-closure glaucoma. A special effort to excise a long segment of optic nerve at the time of enucleation of these cases is suggested.

Summary

Histologic examination of ten intraocular melanomas (eight choroidal and two of the iris and ciliary body) with dispersion of tumor cells into the vitreous body showed optic nerve invasion ranging from only a few collections of tumor cells lying in the anterior portion of the nerve, to invasion of the entire nerve and possibly the chiasm. Nine of the ten melanomas were partially necrotic. Orbital recurrence developed in four cases in which

the tumors extended to the surgically cut margin of the excised optic nerve. All of the eyes had no light perception and had angle-closure glaucoma. In a companion retrospective study of 38 endophytic retinoblastomas with optic nerve invasion, 29 had angle-closure glaucoma. The posterior dispersion of tumor cells, and possibly their optic nerve head invasion, may have been enhanced by the obstruction of the normal anterior segment aqueous outflow channels and the associated glaucoma.

ACKNOWLEDGMENT

George Howard, M.D., and Frederick C. Blodi, M.D., each referred a patient.

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UNINTENTIONAL FILTRATION AFTER CATARACT SURGERY

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An appropriate literary tribute to Michael Hogan should include reports based on correlations of histologic and clinical findings. He has been a proponent of this approach to clinical research and has used it effectively. In 1963, Hogan introduced and was the first editor of a section in the Archives of Ophthalmology entitled "Brief pathologic reports." This valuable section continues as "Clinico-pathologic case reports."

Our present report is concerned with a clinical pathologic study of unintentional filtration after cataract extraction. In 1964, one of us (K.C.S.) and Campbell[1] reported this complication when a limbal incision was inaccurately closed by sutures buried under a limbal-based flap. As compared to aqueous humor leaking directly into the conjunctival sac and thereby causing a flat anterior chamber, we observed these filtrations to be relatively innocuous and often self-correcting. Later studies indicated that filtrations may occur even with the relatively small incisions and with fornix-based as well as limbal-based flaps.[2] Occasionally they cause serious problems. Additional studies of the pathogenesis and prevention of postoperative filtration, therefore, are indicated.

For many years, we have investigated normal and abnormal wound healing in ocular tissues. Important sources of information have been eyes obtained post mortem from patients who underwent surgery here.[3,4]

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CASE REPORT

An 81-year-old man was admitted with visual acuity reduced to light perception by senile cataracts. He had a chronic, mildly obstructive pulmonary disease, controlled congestive heart failure, and rheumatoid arthritis; however, he was ambulatory and mentally alert. He believed that cataract extraction would relieve his total dependence on others. Based on a general physical examination and laboratory and radiologic studies, the patient's general status permitted the surgery under local anesthesia with early postoperative ambulation.

A limbal-based flap of conjunctiva and Tenon's capsule was reflected to the anterior border of the cornescleral limbus in the right eye; the corneoscleral limbus was grooved close to the scleral border and then was shelved forward 0.5 mm. Double-armed 7-0 chromic sutures were placed across the groove, mattress fashion, on the temporal and nasal sides. A single suture was placed though the lips of the groove at 12 o'clock. These sutures were intended to be about halfway through the stroma. At the 1 o'clock position the anterior chamber was entered with a knife cut under the limbal shelf. The incision was enlarged to 180 degrees with scissors. A half-lap type of incision was cut.[5] A sector iridectomy was performed because the lens was unusually large and the pupil dilated poorly. The lens was extracted intracapsularly with a cryoprobe. The previously placed mattress sutures were converted to radial sutures and all five sutures were tied. The conjunctiva and Tenon's capsule then were closed with a continuous 7-0 suture tied at both ends. At the end of the operation the anterior chamber had reformed.

The postoperative course was uncomplicated. The patient had improved vision with an aphakic correction; therefore, the left eye was operated on seven days later, by means of the same technique. The next day, the patient had bouts of severe coughing. For the first time, a diffuse filter was noted in the right eye that had been operated on eight days earlier. The left eye, that had been operated on the previous day, had a boggy flap, but no definitie filtration. In both eyes the anterior chambers were deep and clear.

Two days after the second operation, the patient had a fever, increased sputum, and dyspnea. His white blood cell count was elevated, and a chest x-ray film revealed increased density of the bronchopulmonary tree. The patient died the next day of bronchopneumonia. The right eye, ten days after surgery, had a diffuse filtration under the conjunctival flap and Tenon's capsule. The left eye, three days after surgery, also appeared to be developing a filter. In each eye, the cornea, anterior chamber, and vitreous cavity were clear. The vitreous face was intact and behind the pupils. Both anterior chambers had normal aphakic depth. There were no appreciable abnormalities of the fundus.

RESULTS

Autopsy confirmed the clinical diagnosis of bronchopneumonia. Both eyes were obtained post mortem to correlate the clinical picture of postoperative filtration with the microscopic appearance of the wounds. Gross inspection of the left eye removed three days after surgery showed that the conjunctival flap and Tenon's capsule were slightly distended by fluid at the 11 to 1 o'clock position. This area of apparent filtration was centered around the central limbal suture. The limbal wound edges appeared to be in good apposition.

When the eye was calotted, the iris was in the usual aphakic position. Examination of the angle under a dissecting microscope revealed no incarceration of iris in the wound. We noted some blood on the ciliary body superiorly, although there had been no clinical evidence of bleeding. The vitreous cavity was jelled with the face intact and well behind the pupil. Histologically, we sectioned the globe vertically through the areas of maximal filtration. Microscopic studies of the three-day specimen confirmed the clinical observation of a developing filtration (Fig. 1). There was separation of the subepithelial fibers by fluid at the 12 o'clock position, but there was sealing of deeper layers to the sclera. In contrast, the stromal wound still appeared inert. The leakage of fluid centered around a single suture. The suture loop involved almost the full thickness of the limbal stroma. The innermost layer of the stroma including Descemet's membrane was buckled into the anterior chamber thereby producing a posterior gaping of the wound. The inner side of the loop of the suture was directly exposed to the aqueous humor, but at this stage, the collagen fibers ap-

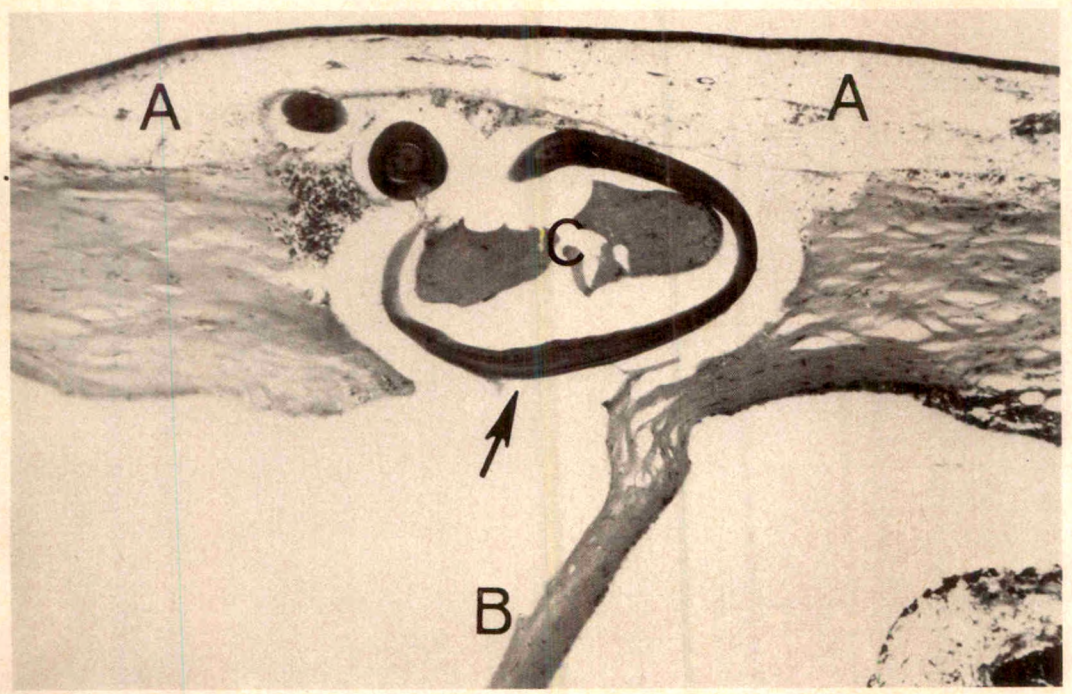


Fig. 1 (Swan and Jones). Postmortem specimen with filtration obtained three days after cataract extraction. Subepithelial tissue (A) is separated by aqueous fluid, but the deeper layers already are adhering to the underlying sclera. A suture (arrow) has buckled open the deeper layers (B) of the half-lap incision. Tissue (C) within the loop is crushed by the too tightly tied suture (hematoxylin and eosin, ×40).

peared intact and inert. The knot appeared to be tied too tightly, resulting in crushing of the stroma within the loop as evidenced by loss of structure. In sections adjacent to the deeply placed and tightly tied suture, both posterior gaping of the wound and overriding of the wound edges were evident (Fig. 2).

Gross inspection of the right eye (Fig. 3) ten days after surgery revealed the conjunctival incision to be tightly adherent to the sclera and limited the filtration to the flap. Clinically the filtration appeared to develop superiorly between two sutures. In the gross specimen this also was the area of maximal elevation of the conjunctiva. The five limbal sutures appeared intact under the edematous conjunctiva and Tenon's capsule.

There were several relevant histologic findings in the ten-day-old specimen. The subepithelial connective tissue of the flap was separated by fluid in the typical manner of a functioning filter (Fig. 4). Deeper layers of the fluid-distended flap were firmly attached to the sclera to the edges

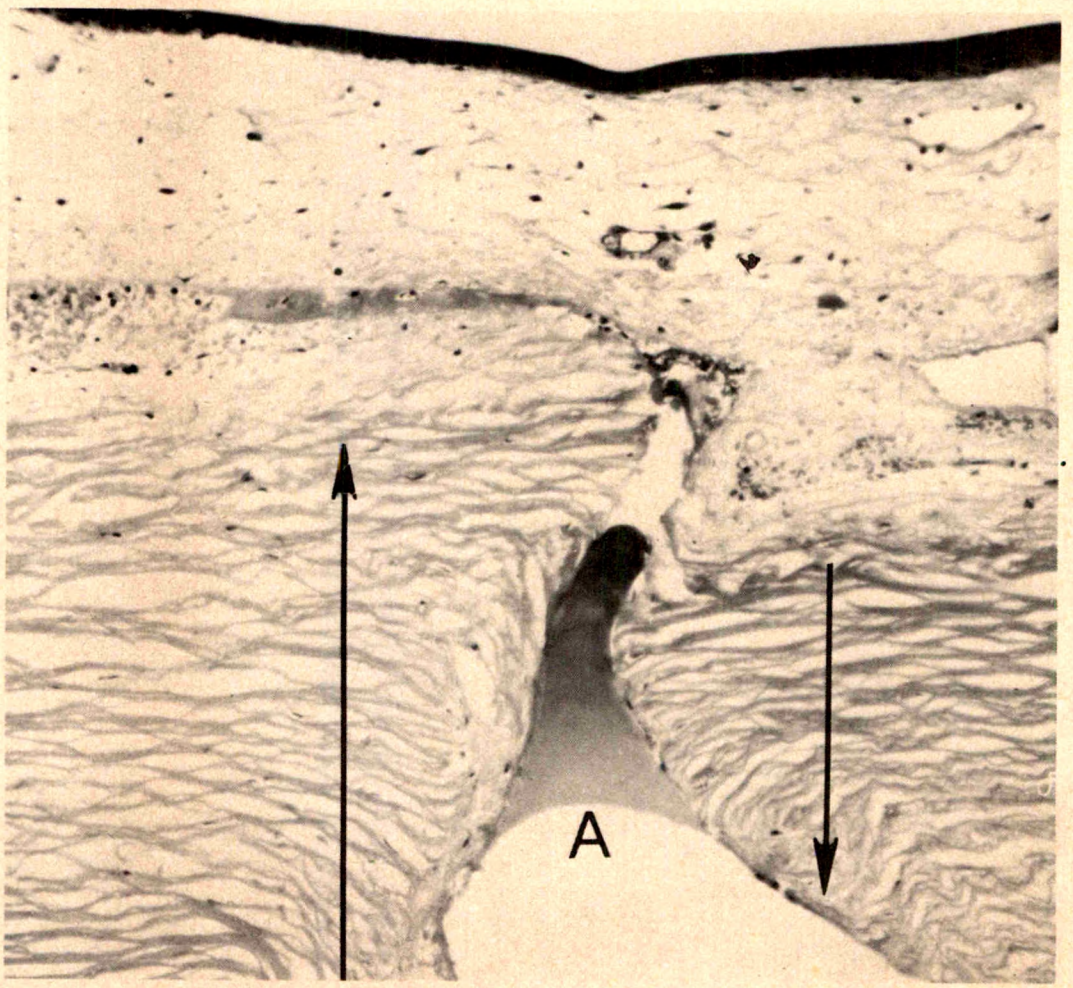


Fig. 2 (Swan and Jones). The tightly tied suture shown in Figure 1 has caused overriding of the limbal wound edges (arrows). A dark-staining, protein-rich fluid (A) partially fills the posterior gap in the wound (hematoxylin and eosin, ×100).

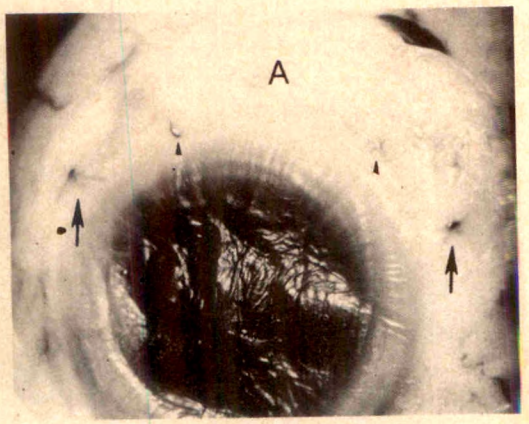


Fig. 3 (Swan and Jones). Gross appearance of postmortem specimen obtained ten days after cataract extraction. The conjunctival flap (A) is distended by aqueous fluid obscuring underlying limbal sutures. Limbal sutures (arrows) appear intact.

of the stromal incision, even to where it was separated. There was no histologic evidence of appreciable cellular activity in the edges of the stromal wound. This finding was in accordance with the findings reported by Flaxel and Swan.[3] They observed that the healing of stromal wounds was by ingrowth of connective tissue from the subepithelial layers, but that this ingrowth usually did not extend through the full width of the stroma until about two weeks after surgery, whereas the healing of the subepithelial tissues in the conjunctiva occurred earlier. In other sections of the eye we studied, ingrowth of subepithelial connective tissue into the limbal wound was just beginning at ten days.

Discussion

Although there was almost no cellular reaction in the stromal wound, there was some inflammatory cell reaction around the collagen sutures (Fig. 4). These sutures were disintegrating and obviously had lost their tensile strength. Clinically and in the gross specimen (Fig. 3), they appeared intact on the day of death.

In both specimens, clinical and histologic studies indicated that the limbal wound separation occurred around or between sutures and was not due to iris or other tissue incarceration in the wound; also, effective closure of the conjunctiva and Tenon's capsule evidently had confined the escaping aqueous humor to the subepithelial tissues of the flap and thereby had prevented anterior chamber collapse. In both eyes, Tenon's capsule had been sutured along with the conjunctiva. Sealed to the episclera, these layers added considerable support to the unhealed limbal wound when it was put under unusual stress by repeated episodes of violent coughing.

In both eyes, the incisions started in the corneoscleral limbus and entered the anterior chamber through the peripheral cornea so that the trabecular zone was undisturbed by the operation. The intact vitreous face was not in contact with the iris in the periphery of the coloboma so that good communication between the posterior and anterior chambers was maintained. This also contributed to the maintenance of the anterior chamber after surgery, despite some leakage of fluid into the filtration bleb.[6]

In the three-day specimen, the escape of aqueous humor from the anterior chamber occurred around a deeply placed and too tightly tied suture that buckled the stromal wound and crushed the tissues. In the ten-day specimen, the site of wound separation was between sutures. These findings support the observations that unintentional filtrations result from poor wound apposition between and around sutures, rather than from tissue incarcerations.[1]

The stromal wound which is precariously weak for at least two weeks should be exactingly closed with suture material that will retain its tensile strength for this critical period. In the three-day specimen, chromic collagen suture was intact, but in the ten-day specimen, considerable disintegration already had taken place.

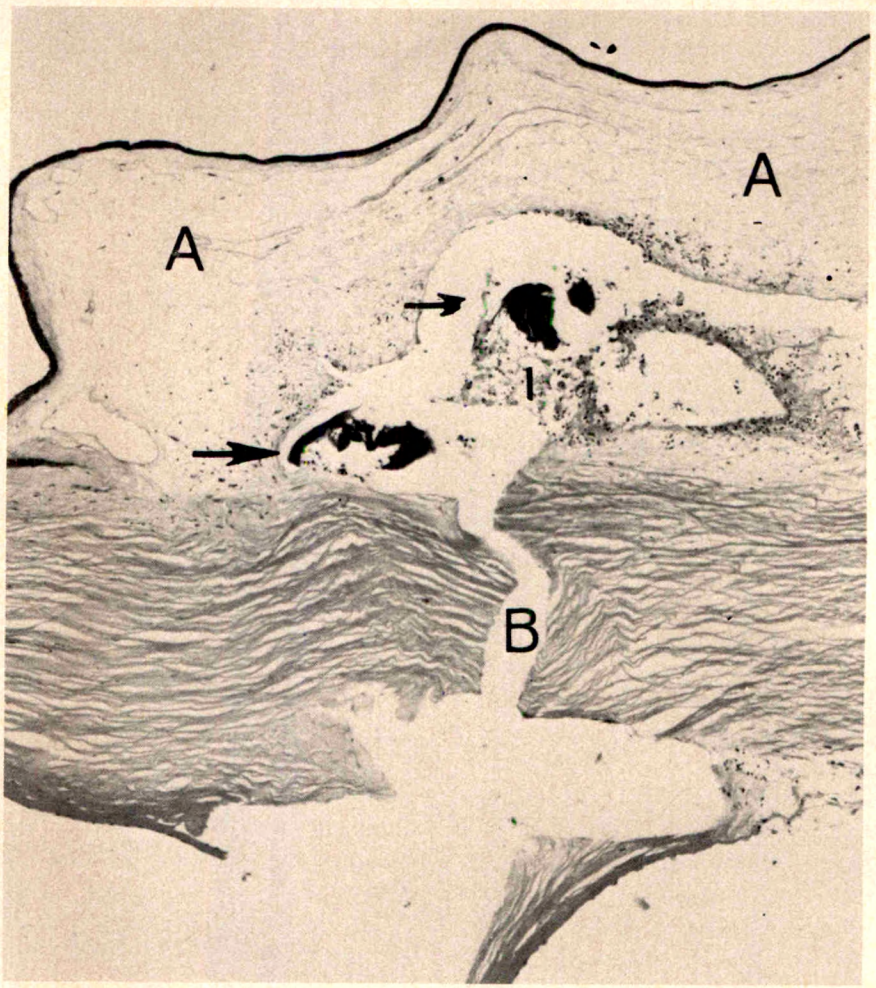


Fig. 4 (Swan and Jones). Microscopic appearance of the specimen shown in Figure 3. Superficial layers of the flap are distended by fluid (A), but the deeper layers of subepithelial tissue are adherent to the stroma. Only fragments of suture (arrows) remain although clinically and in gross specimen (Fig. 3), they appeared intact. Edges of the stromal wound (B) appear inert (hematoxylin and eosin, ×40).

Although they appeared intact clinically, these sutures provided no support to the as yet unhealed stromal wound.

Summary

The eyes of an 81-year-old man were obtained three and ten days after intracapsular extractions had been made through limbal incisions under limbal-based flaps of conjunctiva and Tenon's capsule. The wounds were closed with 7-0 chromic collagen. Before death from bronchopneumonia, the patient developed bilateral filtrations in association with violent coughing spells. In both specimens, the healing processes of the conjunctiva and Tenon's capsule were advanced, confining the escaping aqueous humor to the subepithelial tissues of the flap. In contrast, the stromal wounds were still inert in accordance with our earlier observations that these wounds are precariously weak during the first two weeks after surgery. In cataract surgery,

flaps including both conjunctiva and Tenon's capsule should be prepared and closed to support the slower healing stromal wound.

Prevention of filtrations is not a simple matter of using many sutures. This patient's eyes demonstrated that improperly placed or too tightly tied sutures may be directly responsible for leaking wounds.

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COMPARISON OF IN VITRO CORTICOSTEROID RESPONSE IN PIGMENTARY GLAUCOMA AND PRIMARY OPEN-ANGLE GLAUCOMA

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In 1949, Sugar and Barbour[1] first described pigmentary glaucoma as a separate entity. It was distinguished clinically from primary open-angle glaucoma by the presence of marked pigment dispersion in the anterior segment of the eye,[1] and associated concentric atrophy of the mid-peripheral portion of the iris pigment epithelium, often demonstrable on iris transillumination.[2] Pigment released from the atrophic posterior iris and carried forward by the flow of aqueous humor was found on the zonules and circumference of the lens, the corneal endothelium (Krukenberg's spindle), anterior iris surface, and the filtering portion of the trabecular area.

Controversy has existed as to whether or not pigmentary glaucoma is etiologically separate from primary open-angle glaucoma. Those supporting a separate cause for pigmentary glaucoma have felt that the development of this glaucoma is secondary to mechanical obstruction of the outflow channels by pigment alone,[3–6] or in combination with abnormalities of the angle structures.[7–9] In support of this concept, the severity of the glaucoma has been correlated with the degree of pigmentation.[6] In addition, pigmentary glaucoma generally occurs in younger patients than does primary open-angle glaucoma, and shows a marked predilection for men while primary open-angle glaucoma shows no sex predilection.[3]

On the other hand, those supporting a common etiology for the outflow obstruction in these glaucomas have implied that trabecular pigment deposition is a consequence rather than a cause of aqueous obstruction, and that the occurrence of pigment releasing iris atrophy merely makes the pigment accumulation more dramatic. In support of this view, occasional pigment deposition occurs in the absence of iris atrophy in one half[1] to two thirds[10] of primary open-angle glaucoma patients, and also in patients with secondary glaucoma due to uveitis or trauma.[11,12] Further, the adequacy of pigment alone to obstruct aqueous outflow is questionable since 90% of persons with pigment dispersion, manifested by Krukenberg's spindles, did not have glaucoma.[3,8]

Becker and Podos[12] reported the occurrence of pigmentary glaucoma and primary open-angle glaucoma in the same families, suggesting a common genetic basis. They also examined topical corticosteroid response in 15 persons with Krukenberg's spindles without glaucoma, and found more corticosteroid responders than in the general population. The corticosteroid responses of the patients with Krukenberg's spindles approximated those of the offspring and siblings of primary open-angle glaucoma patients, suggesting a link of pigment disperson to corticosteroid responsiveness and primary open-angle glaucoma.

We evaluated the possible relationship of pigmentary glaucoma to primary open-angle glaucoma by comparing in vitro cellular sensitivity to corticosteroid in the two groups, as assayed by inhibi-

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tion of lymphocyte transformation. Previous results of this assay correlated well with those of ocular corticosteroid testing, and demonstrated a markedly increased sensitivity to corticosteroids at the cellular level in primary open-angle glaucoma.[13,14] Use of a nonocular assay allowed study of corticosteroid sensitivity in persons whose spontaneous intraocular pressures would have been too elevated to permit meaningful topical testing. It avoided the potential problem that in topical testing the presence of pigment in the trabecular region may augment the apparent response to corticosteroid.

Subjects and Methods

Twenty patients with pigmentary glaucoma had elevated intraocular pressures before treatment, gonioscopically open angles, and evidence of pigment dispersion including Krukenberg's spindles and heavy trabecular pigmentation. Ten had iris transillumination defects. All had visual field loss characteristic of glaucoma, and most had appreciable cupping of the optic nerve head. All but one (newly diagnosed) were receiving medical therapy for their glaucoma at the time of testing. Only one was receiving acetazolamide. There were 16 men and four women. The men averaged 49 ± 14 (σ) years of age at testing, and 41 ± 15 years at diagnosis. The women averaged 40 ± 15 years of age at testing and 38 ± 15 years at diagnosis. Eighteen of the patients were myopic, although only five had myopia greater than 5 diopters. Four patients had a contributory family history of glaucoma, with two known to be primary open-angle glaucoma (Table 1).

The technique for preparation of lymphocyte cultures, corticosteroid preincubation, phytohemagglutinin stimulation, cell harvesting, scintillation counting, and data analysis have been described.[13,14] We determined the concentration of prednisolone-21-phosphate required to inhibit tritiated thymidine uptake in mitogen-transformed cells by 50% (half inhibition concentration, or I_{50}) for each patient. Patient data were accepted for the study if they met the following three criteria. First, the coefficient of variation of the phytohemagglutinin-P stimulated controls was 20% or less. Second, the uptake of tritiated thymidine was 10% or less of the total amount present. Third, the correlation coefficient, r, for the regression analysis of the dose-response curve was .75 or greater.

Results

We obtained the distribution of I_{50} values for each of the patients with pigmentary glaucoma, and for 100 other patients[14] (Figure). The previously reported patients included 36 patients with primary open-angle glaucoma. We classified the rest by topical ocular dexamethasone testing (application of 0.1% dexamethasone-21-phosphate eyedrops to one eye, four times daily, for six weeks). Based on Becker's criteria, these included:

- 22 NN individuals: low responders, whose final intraocular pressure remained < 20 mm Hg.
- 15 NG individuals: intermediate responders, whose final intraocular pressure was between 20 and 31 mm Hg.
- 27 GG individuals: high responders, whose final intraocular pressure was > 31 mm Hg.

We studied these 100 patients during the present study.

In the lymphocyte assay, the lower the I_{50} value obtained, the more sensitive is the individual to corticosteroids. Means for each group in the Figure are noted by a horizontal bar. The primary open-angle glaucoma and GG groups had nearly equal mean sensitivities, and greater mean sensitivity than NG patients, who in turn had greater mean sensitivity than NN patients. Pigmentary glaucoma patients exhibited a wide range of I_{50} values,

TABLE 1

CLINICAL DATA

Case No.	Age, yrs	Race	Sex	Age at Onset, yrs	Family History	Refraction	Visual Acuity	Visual Fields	Krukenberg's Spindles	Heavy Trabecular Pigmentation	Iris Transillumination Defects	I_{50}†
1	39	W	F	31	–	RE: −3.75	20/70	Central island	+	+	–	96
						LE: −1.25 + 0.25 × 180°	20/20	Normal				
2	44	W	M	44	–	RE: plano	20/30	Normal	+	+	+	53
						LE: −9.50 + 2.00 × 180°	20/80	Inferior Bjerrum				
3	60	W	M	45	–	RE: −2.00	HM	Temporal island	+	+	+	72
						LE: −2.50	20/20	Superior Bjerrum				
4	47	W	M	43	–	RE: −1.25 + 0.25 × 110°	20/30	Superior Bjerrum	+	+	+	60
						LE: −1.75	20/20	Normal				
5	62	W	F	61	+	RE: −0.75 + 0.75 × 45°	20/25	Normal	+	+	–	61
						LE: −0.75 + 0.75 × 140°	20/20	Inferior Bjerrum				
6	28	W	F	28	–	RE: −3.25 + 1.25 × 180°	20/15	Nasal step	+	+	+	61
						LE: −2.75 + 0.75 × 180°	20/15	Normal				
7	69	W	M	69	–	RE: +0.75	20/200	Superior Bjerrum	+	+	–	51
						LE: +0.75	20/70	Superior Bjerrum				
8	24	W	M	23	–	RE: −7.00 + 1.00 × 5°	20/20	Superior Bjerrum, nasal step	+	+	+	57
						LE: −6.00 + 1.00 × 160°	20/20	Nasal step				
9	43	W	M	35	–	RE: −7.75 + 1.25 × 90°	20/20	Normal	+	+	–	62
						LE: −7.50	20/25	Blind spot elongation				
10	55	W	M	43	+	RE: −2.75 + 0.75 × 180°	20/20	Normal	+	+	–	74
						LE: −2.75 + 0.75 × 170°	20/20	Superior nasal step				
11	48	W	M	30	+	RE: −0.50 + 0.25 × 180°	20/20	Bjerrum	+	+	–	101
						LE: plano	20/20	Normal				
12	65	B	M	63	–	RE: +0.50	20/20	Inferior nasal loss	+	+	–	68
						LE: +1.00	20/20	Inferior nasal loss				
13*	29	W	M	29	–	RE: −4.00	20/20	Inferior arcuate	+	+	+	87
						LE: −4.00	20/20	Inferior arcuate				
14	34	W	F	33	–	RE: −3.75 + 0.50 × 125°	20/20	Nasal step	+	+	+	60
						LE: −4.25 + 1.25 × 180°	20/30	Superior and inferior Bjerrum				
15	55	W	M	33	–	RE: −2.25	20/25	Superior Bjerrum	+	+	+	15
						LE: −2.00 + 0.25 × 5°	20/20	Normal				
16	58	W	M	56	–	RE: −0.75 + 1.50 × 180°	20/20	Superior Bjerrum	+	+	–	81
						LE: −1.25 + 1.75 × 180°	20/20	Inferior Bjerrum				
17	49	W	M	40	–	RE: −6.00	20/25	Superior and inferior Bjerrum	+	+	+	72
						LE: −7.00	20/20	Inferior Bjerrum, nasal step				
18	50	W	M	56	+	RE: −12.50 + 1.25 × 100°	20/100	Superior and inferior Bjerrum	+	+	–	23
						LE: −11.00 + 0.50 × 180°	20/30	Superior Bjerrum				
19	62	W	M	22	–	RE: −2.75 + 0.25 × 65°	20/25	Normal	+	+	+	60
						LE: −4.00	20/400	Central island only				
20	22	W	M	21	–	RE: −4.00 + 0.75 × 160°	20/20	Paracentral scotoma	+	+	+	39
						LE: −4.00 + 0.50 × 40°	20/20	Normal				

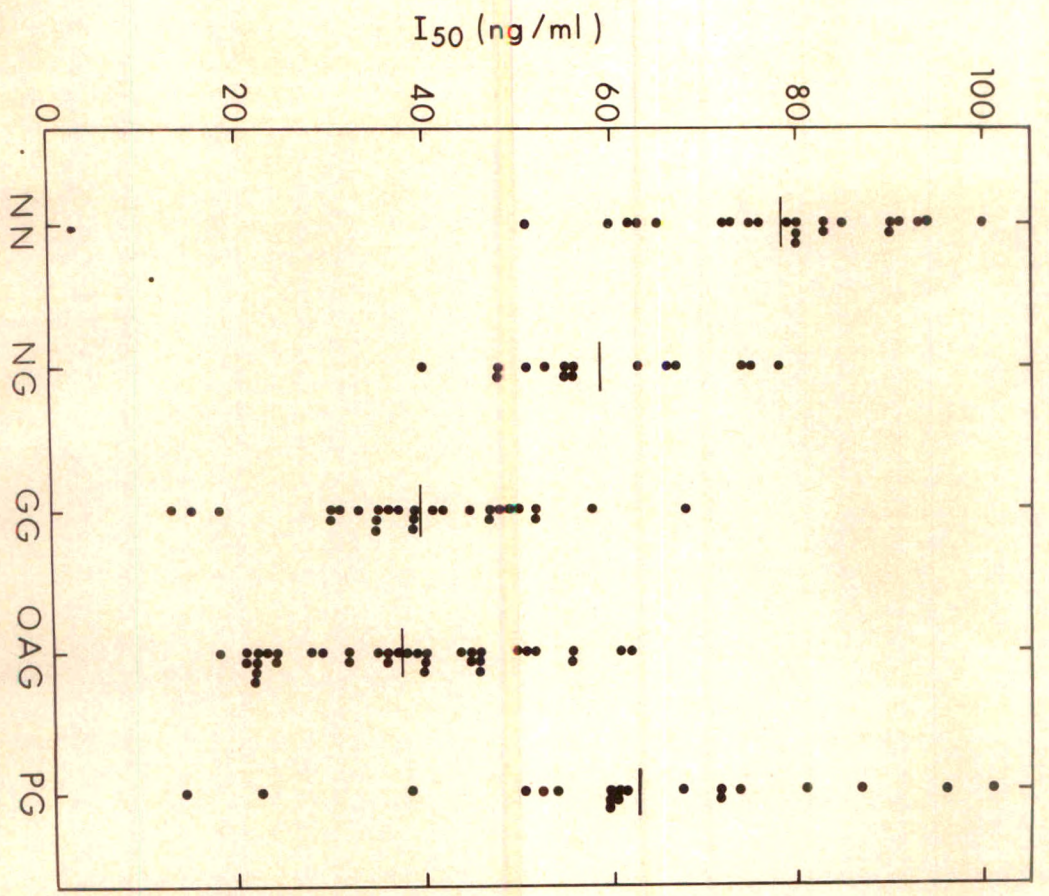


Figure (Zink and associates). Distribution of I_{50} values by categories of topical dexamethasone low responder (NN), intermediate responder (NG), high responder (GG), primary open-angle glaucoma (OAG), and pigmentary glaucoma (PG).

and a mean I_{50} that was between the NN and NG means. Table 2 summarizes the data numerically, and notes the significant difference in sensitivity ($P < .001$) between the pigmentary glaucoma and primary open-angle groups. There were significant differences in sensitivity between the pigmentary glaucoma group and both the NN ($P < .01$), and GG ($P < .01$) groups, but no significant difference between the pigmentary glaucoma group and the NG group.

We found no significant correlation among the patients with pigmentary glaucoma between I_{50} and a positive family

TABLE 2

PREDNISOLONE-21-PHOSPHATE INHIBITION OF LYMPHOCYTE TRANSFORMATION BY OCULAR CLASSIFICATION

Classification*	No.	Mean I_{50}	Standard Deviation
NN	22	78.41	12.55
NG	15	59.00	11.10
GG	27	39.44	12.45
POAG	36	37.25	12.50
PG	20	62.65	21.19

*POAG, primary open-angle glaucoma; PG, pigmentary glaucoma.

history of primary open-angle glaucoma, myopia greater than five diopters, a diagnosis of glaucoma made at > 40 years of age, the presence of iris transillumination defects, or the city (Detroit or St. Louis) where the patient was treated (Table 3).

Discussion

The etiologies of pigmentary glaucoma and primary open-angle glaucoma are unknown. In the case of primary open-angle glaucoma, however, there is circumstantial evidence that increased sensitivity to corticosteroids may play a role in the pathogenesis of the disease. Corticosteroids applied to the eyes of susceptible persons lead to marked elevation of intraocular pressure, decreased outflow facility, optic nerve head cupping, and characteristic glaucomatous visual field loss, thus mimicking primary open-angle glaucoma.[15] While marked pressure elevations (to > 31 mm Hg) may be elicited by topical corticosteroids in 82% of patients with primary open-angle glaucoma, only 6% of the general population responds in this manner.[16,17]

The association of primary open-angle glaucoma and increased sensitivity to corticosteroids also holds on the cellular level. In vitro determination of sensitivity to corticosteroid by assay of inhibition of lymphocyte transformation yielded results that correlated well with topical testing results (correlation coefficient, $r = .81$),[14] and showed significantly increased sensitivity to corticosteroids in patients with primary open-angle glaucoma.[13,14]

TABLE 3

PIGMENTARY GLAUCOMA SUBGROUPS

Subgroup	No.	Mean I_{50}	I_{50} of others*
Family history of glaucoma	4	65 ± 32	62 ± 19
Myopia > 5 diopters	5	53 ± 18	66 ± 22
Age at diagnosis > 40 years	9	64 ± 10	61 ± 28
Iris transillumination defects	10	58 ± 20	68 ± 22
From St. Louis	12	59 ± 16	68 ± 28

*Patients from Detroit.

If pigmentary glaucoma were merely a variant of primary open-angle glaucoma, we would expect to find a similar degree of increased sensitivity to corticosteroid. Contrarily, as a group, these 20 pigmentary glaucoma patients did not manifest markedly increased sensitivity to corticosteroids. The mean I_{50} for the pigmentary glaucoma patients was 63 ± 21 ng/ml, vs. 37 ± 12 for the primary open-angle glaucoma patients (Table 2). The difference is significant ($P < .001$ by two-tailed t test).

While the pigmentary glaucoma patients were not as sensitive as primary open-angle glaucoma patients, the question arises whether or not they are more sensitive than the general population. A direct answer is not available. We are studying 100 randomly selected subjects to characterize the response of the general population, but sufficient data have not been collected. We may, however, estimate the average response of the general population based on the results for the NN, NG, and GG patients already tested (Table 4).[18] That average I_{50} is 69 ng/ml, slightly higher than the value of 63 ng/ml for the pigmentary glaucoma patients.

We can assess the corticosteroid sensitivity of either the primary open-angle glaucoma or pigmentary glaucoma patients by classifying the in vitro responses into three arbitrary categories corresponding to the three topical response categories. The boundaries for these in vitro categories are obtained from the regression line for I_{50} vs. final pressure achieved.[14] The dividing points of ocular testing, at 20 and 31 mm Hg, correspond to in vitro I_{50} values of 71 and 51 ng/ml, respectively. The distribution of low, in-

TABLE 4

ESTIMATION OF THE MEAN I_{50} FOR THE GENERAL POPULATION

Category	I_{50}	% of General Population		Contribution, ng/ml
NN	78.41 ×	58	=	45.48
NG	59.00 ×	36	=	21.24
GG	39.44 ×	6	=	2.37
General population		100		69.09

TABLE 5

DISTRIBUTIONS OF CORTICOSTEROID RESPONDERS

Group	NN, %	NG, %	GG, %
Pigmentary open-angle glaucoma			
Ocular testing	1 (1)	17 (17)	82 (82)
In vitro testing	0 (0)	19 (7)	81 (29)
Pigmentary glaucoma			
In vitro	35 (7)	50 (10)	15 (3)
General population			
Ocular testing	58 (174)	36 (108)	6 (18)

*Numbers in parentheses indicate subjects.

termediate, and high responders, for both ocular[16] and in vitro testing of primary open-angle glaucoma patients, is given in Table 5. The correspondence of the results is good. The distributions for in vitro testing of pigmentary glaucoma patients, and ocular testing of a general population,[17] are listed for comparison. The difference between the distributions for primary open-angle and pigmentary glaucoma patients on in vitro testing is significant ($P < .001$ by chi-square analysis contingency). Assuming the validity of cross-test comparison, it appears there is some enrichment of in vitro corticosteroid responders (intermediate and high) in the pigmentary glaucoma group relative to the general population, but clearly that enrichment is small compared to that seen for the primary open-angle glaucoma group.

A similar enrichment of corticosteroid responders was noted on topical testing of the normal fellow eye of patients with angle recession glaucoma.[19] Presumably, the compromising additive effects of trauma and a latent tendency to primary open-angle glaucoma are sufficient to cause disease, while neither trauma alone (in a similarly injured corticosteroid nonresponder) nor the latent tendency alone (in the similarly responsive but uninjured fellow eye) is sufficient. An analogous postulate may be offered to account for the small enrichment of in vitro responders among the pigmentary glaucoma patients, with additive components of obstruction due to pigment (or angle anomalies) and latent primary open-angle glaucoma.

As a group, pigmentary glaucoma patients do not have the markedly increased sensitivity to corticosteroids seen in patients with primary open-angle glaucoma. If increased sensitivity to corticosteroids plays an essential role in the pathogenesis of primary open-angle glaucoma, then pigmentary glaucoma appears to be etiologically, as well as clinically, a separate entity.

SUMMARY

We used an in vitro assay utilizing corticosteroids to inhibit transformation of peripheral blood lymphocytes to evaluate a group of 20 patients with pigmentary glaucoma. The pigmentary glaucoma patient group did not manifest the markedly increased cellular sensitivity to corticosteroids associated with primary open-angle glaucoma. If increased sensitivity to corticosteroids plays an essential role in the pathogenesis of primary open-angle glaucoma, then pigmentary glaucoma appears to be etiologically, as well as clinically, a separate entity.

ACKNOWLEDGMENTS

Steven Podos, M.D., Theodore Krupin, M.D., Jack Kayes, M.D., Robert Drews, M.D., and Jacob Wilen-

sky, M.D., referred patients. Merck, Sharp and Dohme provided prednisolone-21-phosphate.

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Samuel Johnson, *The History of Rasselas, Prince of Abissinia*
Harvard University Press, 1951

VOLUME 80 NUMBER 3, PART II SEPTEMBER, 1975

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1. Duke-Elder, S.: Diseases of the Outer Eye, Part I, System of Ophthalmology, Vol. VIII, The C. V. Mosby Co., (St. Louis), 1965, p. 68.

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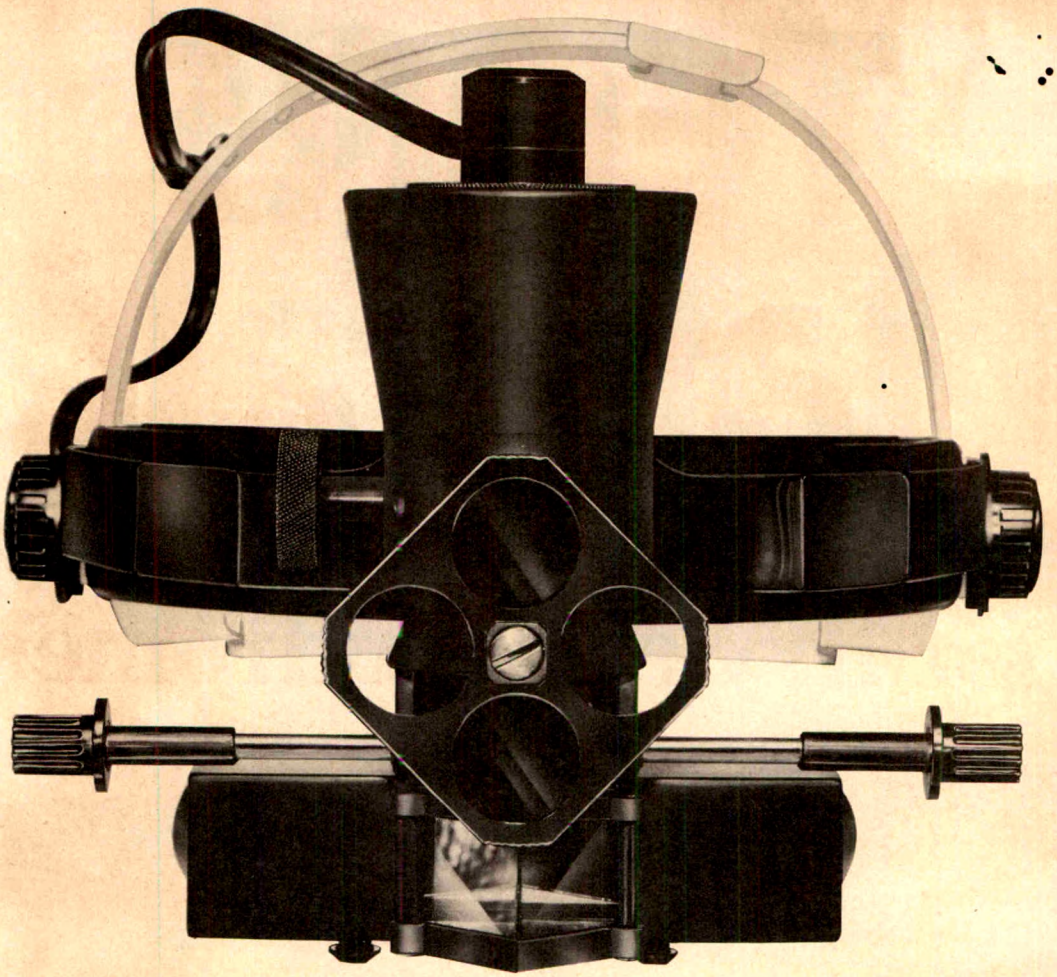


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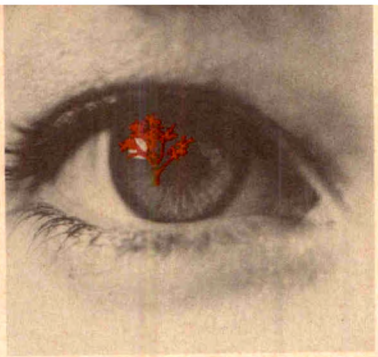
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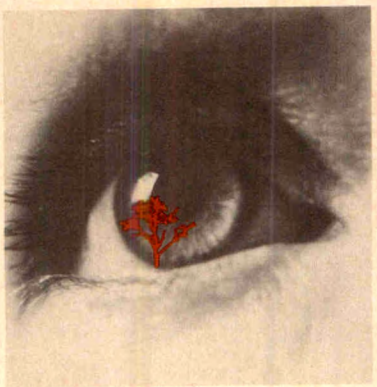
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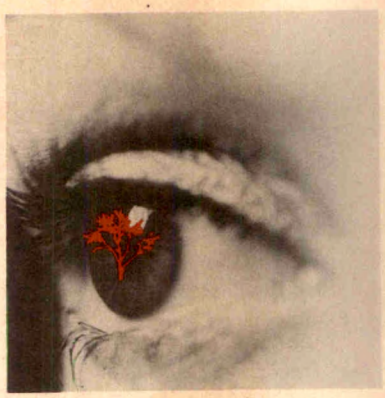
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dications: Only in the treatment of herpes nplex keratitis.

scription: 'Stoxil' Ophthalmic Solution ntains idoxuridine (5-iodo-2 -deoxyuri- ie) 0.1% (1 mg./ml.) in distilled water; rile when packaged. Preserved with thi- erosal, 1:50,000. 'Stoxil' Ophthalmic Oint- ent contains idoxuridine 0.5% (5 mg./gram) a petrolatum base. (White petrolatum and uid petrolatum are inactive ingredients.)

ntraindications: Contraindicated in pa- nts with known or suspected hypersen- vity to any of its components.

arning: Usage in Pregnancy—Idoxuridine ould be administered with caution in preg- ncy or in women of childbearing potential. hough teratogenic effects were reported one study with rabbits when idoxuridine as instilled into the eye, these effects were t observed in a subsequent, more detailed udy, even at doses substantially higher than ose in the preceding study.

ecautions: Some strains of herpes simplex pear to be resistant. If there is no response *epithelial infections* after 7 or 8 days of eatment, other forms of therapy should be nsidered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

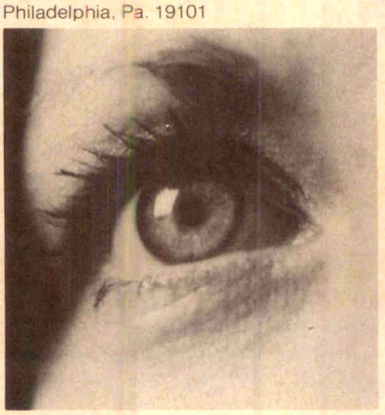
'Stoxil' Ophthalmic Solution should not be mixed with other medications.

Adverse Reactions: Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally, corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

How Supplied: 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

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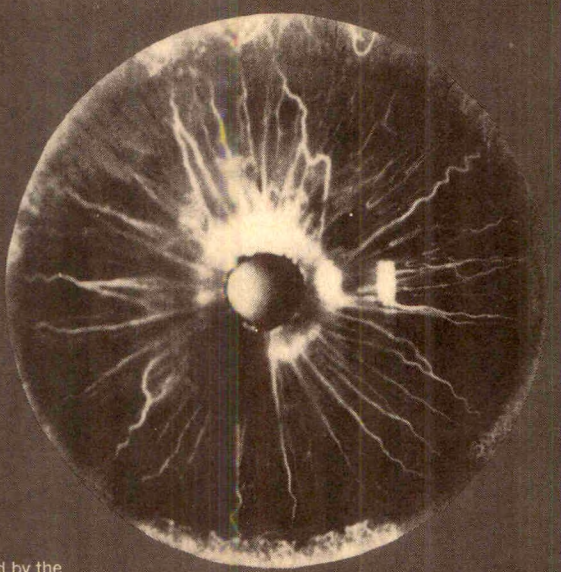
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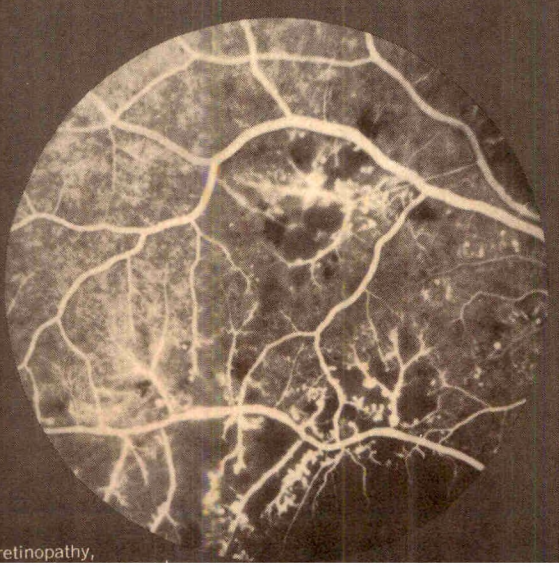
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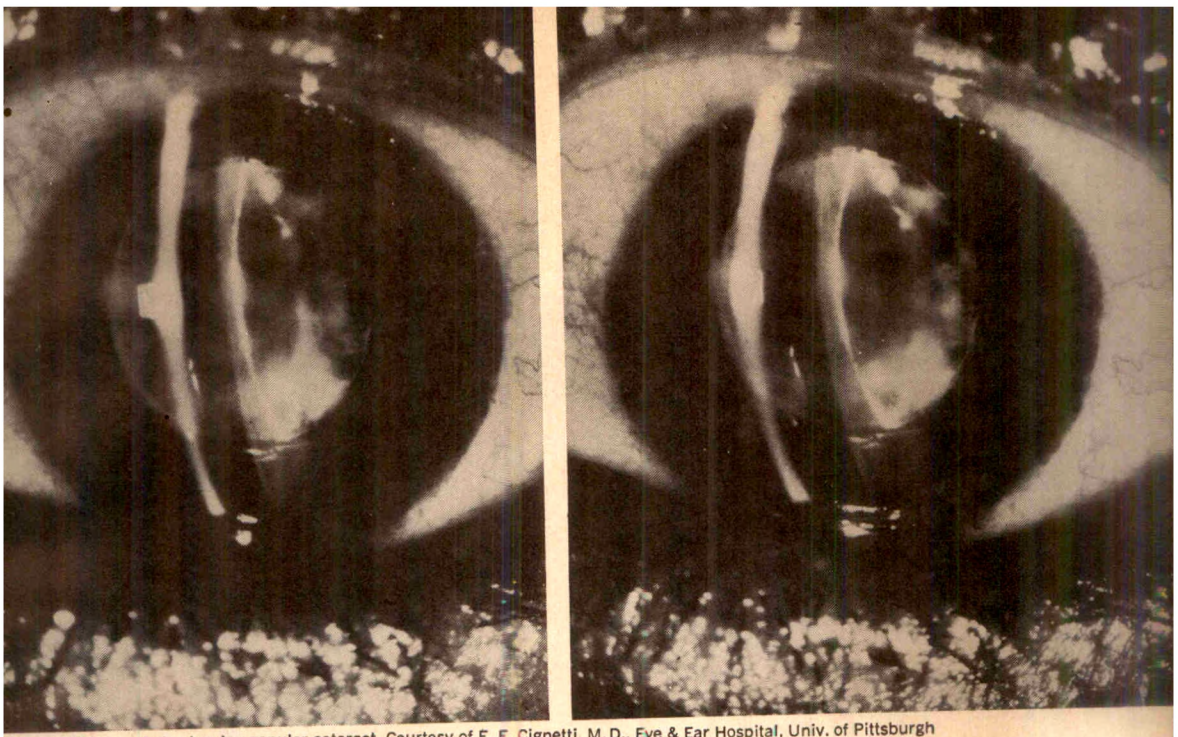
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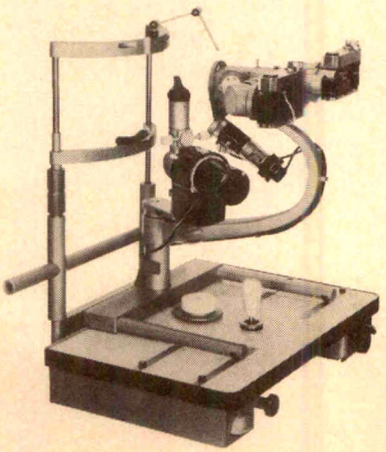
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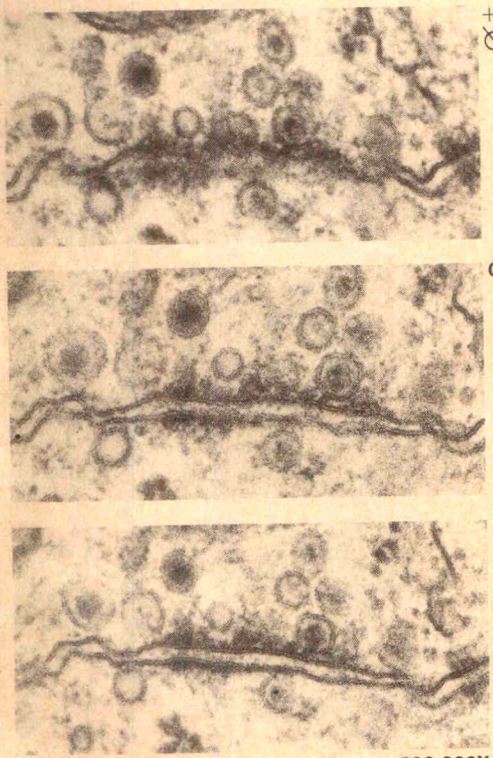
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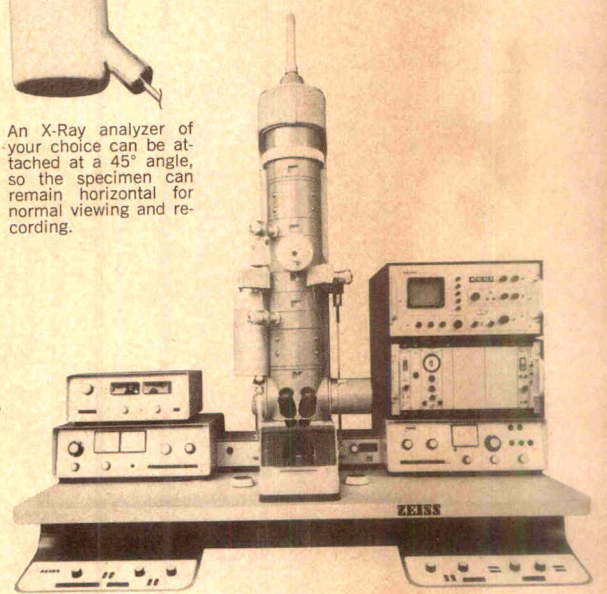
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(If you don't treat it, she will.)

You know a real dry eye when you see it. A post-menopausal arthritic woman with foreign body sensation, diffuse corneal staining and perhaps a positive Schirmer tear test to confirm your diagnosis.



And you know that Liquifilm® Tears can help relieve her discomfort. But what about the patient with the apparent dry eye? The patient who complains of the same uncomfortable dry-eye symptoms although you detect no objective findings?

Liquifilm Tears can help her too.

To the patient with the apparent dry eye it's every bit as irritating as the real thing. So much so that if left untreated, chances are she'll head for the nearest drugstore or supermarket shelf for help.



And here is where do-it-yourself medication can turn an apparent problem into a real one. The eye drop she picks up may be unnecessarily medicated. Or one with an aqueous vehicle capable of actually inducing a dry eye by interfering with the oily layer of the tear film.

You can spare her all that by recommending Liquifilm Tears.

Liquifilm Tears has provided soothing relief from dry-eye symptoms...without creating any new problems...hundreds of millions of times since 1963.

That means more Liquifilm Tears has been recommended by more ophthalmologists than all other tear substitutes, combined.

Recommend Liquifilm Tears for both the real and the apparent dry eye. All it can do is help.

ALLERGAN Irvine, California / Pointe Claire, P. Q., Canada



LIQUIFILM® TEARS.
FOR THE REAL AND THE APPARENT DRY-EYE.

Another Important Step.

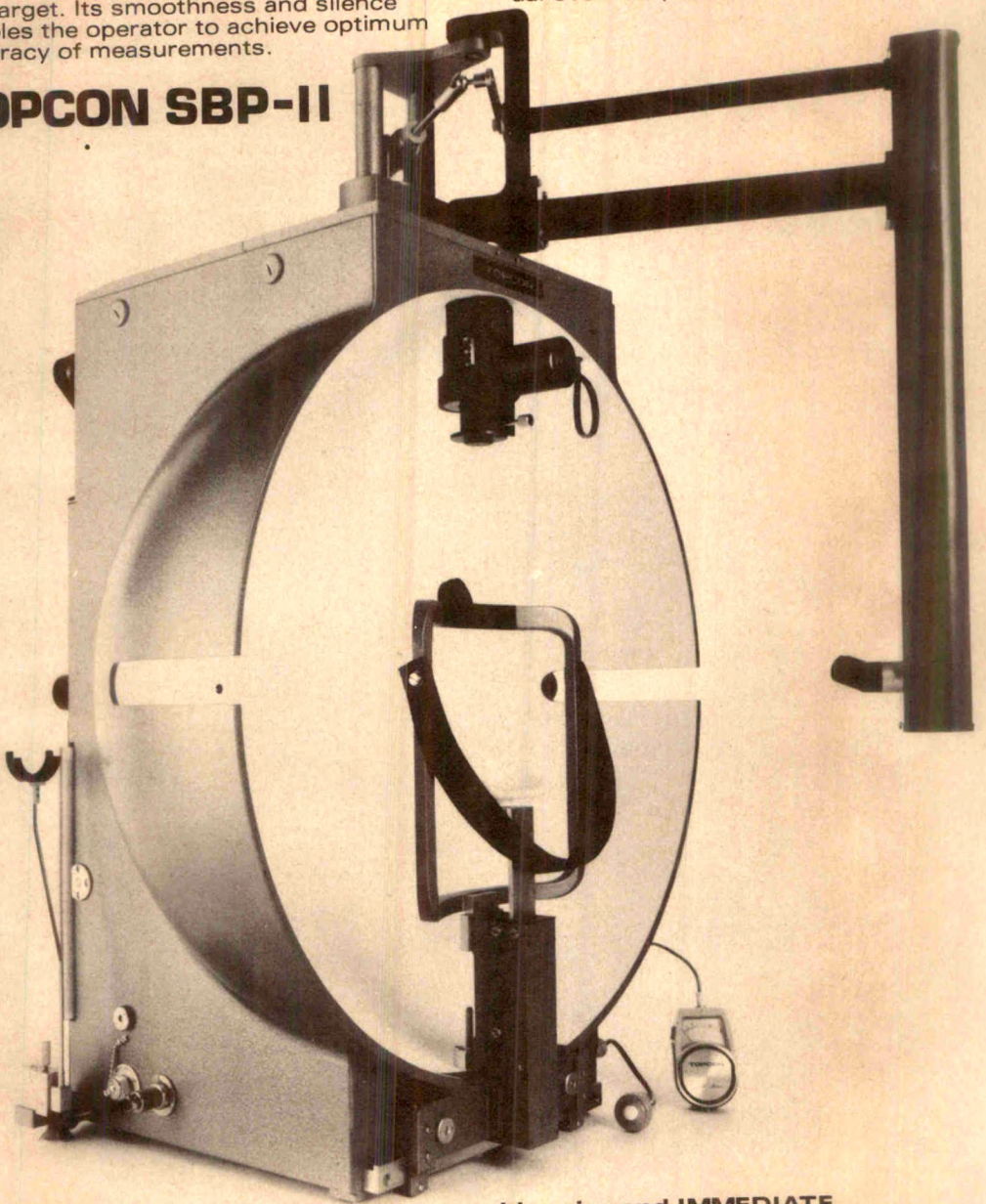
The SBP-11 is recognized for its accuracy and ease of operation in critical perimetry field testing because of our constant monitoring for improvements made possible through new technological developments.

One such improved feature on the SBP-11 is a new device for occluding the target. Its smoothness and silence enables the operator to achieve optimum accuracy of measurements.

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- Constant monitoring of patient's fixation with sighting telescope.
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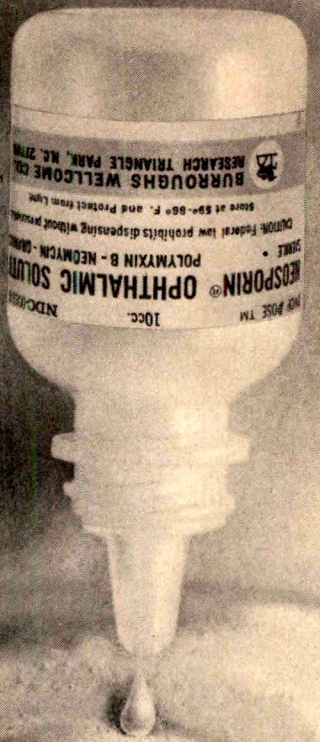
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You may now prescribe Neosporin Ophthalmic Solution in a new plastic bottle...just specify **DD**...a better way of administering solution to the eye.



for bacterial conjunctivitis

Neosporin® Ophthalmic Solution, Sterile

Polymyxin B-Neomycin-Gramicidin

Each cc contains: Aerosporin® brand Polymyxin B Sulfate 5000 units; neomycin sulfate 2.5 mg (equivalent to 1.75 mg of neomycin base); gramicidin 0.025 mg, in a solution containing the inactive ingredients alcohol (0.5%), propylene glycol, polyoxyethylene polyoxypropylene compound, sodium chloride, and purified water (preservative: thimerosal 0.001%). Available in the new 10 cc Drop Dose™ Plastic Dispenser Bottle. Also available in a 10 cc glass bottle with sterile dropper.

Neosporin® Ophthalmic Solution, Sterile
Polymyxin B-Neomycin-Gramicidin

CONTRAINDICATIONS:
This product is contraindicated in those persons who have shown sensitivity to any of its components.

WARNINGS:
Prolonged use may result in overgrowth of nonsusceptible organisms.

PRECAUTIONS:
Culture and susceptibility testing should be performed during treatment.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin.

Complete literature available on request from Professional Services Dept. PML.

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Wanted: Department of Ophthalmology and Visual Science, Assistant or Associate Professor, depending upon experience, background and skill to participate in expanding a resident teaching program and clinical practice in retinal and vitreal disease and corneal and external disease.

When applying please enclose curriculum vitae and bibliography.

We are an equal opportunity employer. Applications from women and minority groups encouraged.

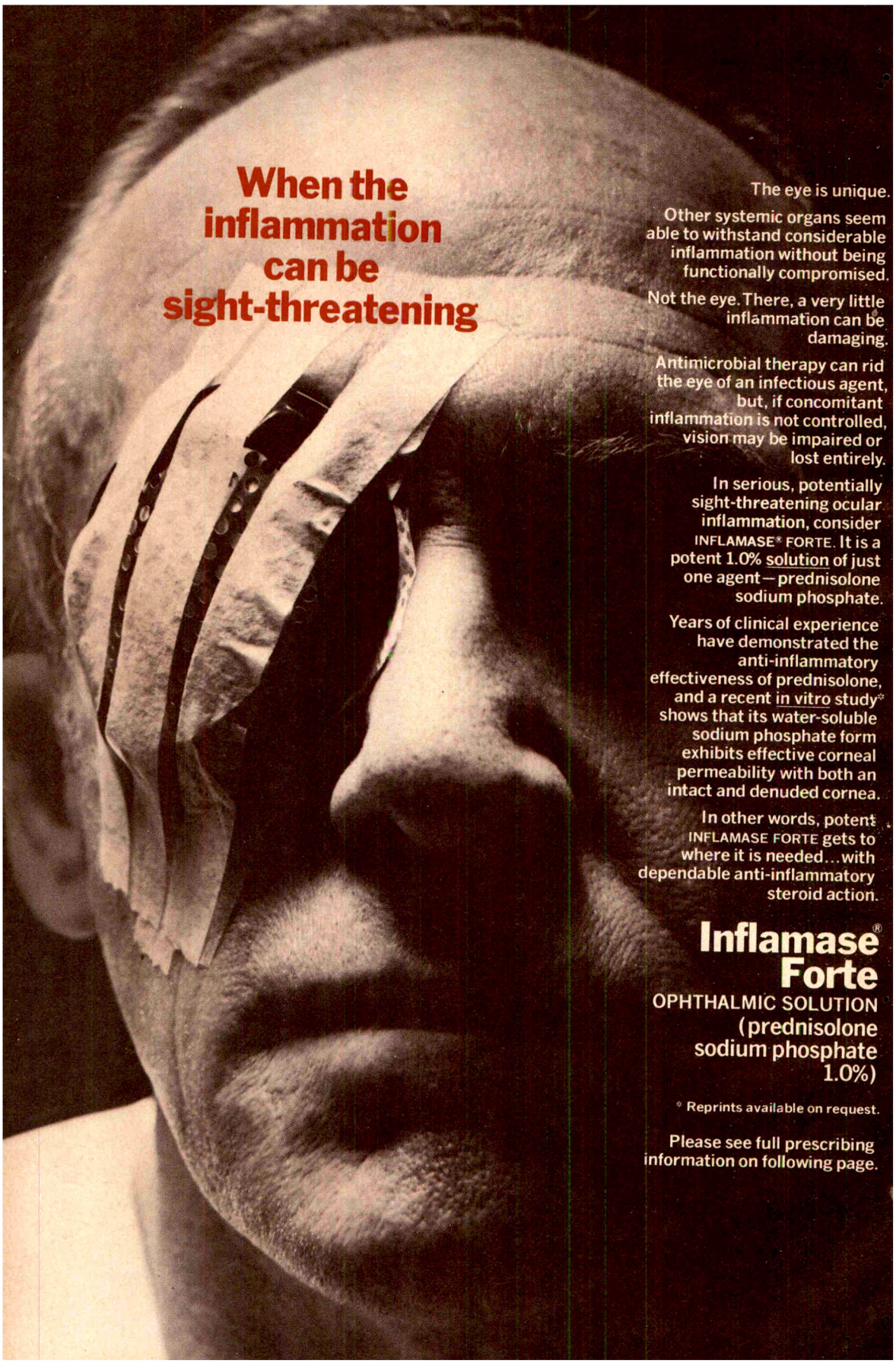
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When the inflammation can be sight-threatening

The eye is unique.

Other systemic organs seem able to withstand considerable inflammation without being functionally compromised.

Not the eye. There, a very little inflammation can be damaging.

Antimicrobial therapy can rid the eye of an infectious agent, but, if concomitant inflammation is not controlled, vision may be impaired or lost entirely.

In serious, potentially sight-threatening ocular inflammation, consider INFLAMASE® FORTE. It is a potent 1.0% solution of just one agent—prednisolone sodium phosphate.

Years of clinical experience have demonstrated the anti-inflammatory effectiveness of prednisolone, and a recent in vitro study* shows that its water-soluble sodium phosphate form exhibits effective corneal permeability with both an intact and denuded cornea.

In other words, potent INFLAMASE FORTE gets to where it is needed...with dependable anti-inflammatory steroid action.

Inflamase® Forte

OPHTHALMIC SOLUTION
(prednisolone sodium phosphate 1.0%)

* Reprints available on request.

Please see full prescribing information on following page.

Inflamase® Forte

OPHTHALMIC SOLUTION
(prednisolone sodium phosphate 1.0%)

Description: Sterile ophthalmic solution having the following composition:
*Prednisolone sodium phosphate: 1.0%
(equivalent to prednisolone 0.8%)
Benzalkonium chloride: 0.01%
in an aqueous, buffered, isotonic solution containing disodium edetate, mono and dibasic sodium phosphate, and sodium chloride.
*Licensed under patent #3,134,718.
Action: Inhibition of inflammatory response to most inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced.
Indications: Steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies. Inflamase Forte Ophthalmic Solution is recommended for moderate to severe inflammations.
In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.
Contraindications: Acute superficial herpes simplex keratitis, fungal diseases of ocular structures, vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, tuberculosis of the eye, hypersensitivity to a component of this medication.
Warnings: Employment of steroid medication in the treatment of stromal herpes simplex keratitis requires great caution; frequent slit-lamp microscopy is mandatory.
Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from pathogens liberated from ocular tissues.
In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by presence of steroid medication.
Topical steroids are not effective in mustard gas keratitis and Sjögren's keratoconjunctivitis. Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated.
If irritation persists or develops, patient should be advised to discontinue use and consult prescribing physician.
Precautions: As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use.
Intraocular pressure should be checked frequently.
This product is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of the bottle. Keep bottle tightly closed when not in use. Store in cool place. Protect from light.
Adverse Reactions: Glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infections from pathogens liberated from ocular tissues, perforation of the globe.
Dosage: Initially, 1 or 2 drops placed in conjunctival sac every hour during day and every 2 hours during night until improvement occurs. Thereafter, 1 or 2 drops, 2 to 4 times daily.
Caution: Federal law prohibits dispensing without prescription.
How Supplied: 5 ml. plastic squeeze bottle with dropper tip.
Also available as Inflamase (prednisolone sodium phosphate) 1/8%.

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on

DIABETES AND DIABETIC RETINOPATHY

to be held on

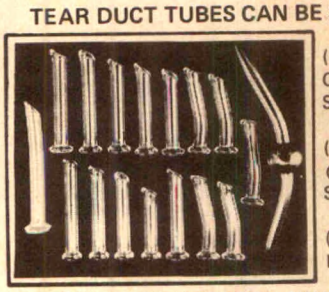
March 12-13-14, 1976

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Irvin M. Kalb, M.D.
Foundation for Ophthalmic Education
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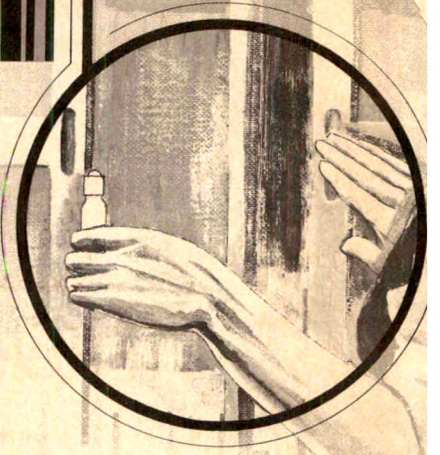
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*L. T. JONES, M.D. DACRYOCYSTORHINOSTOMY, AMERICAN JOURNAL OF OPHTHALMOLOGY, VOLUME 59, NO. 5, MAY 1965.





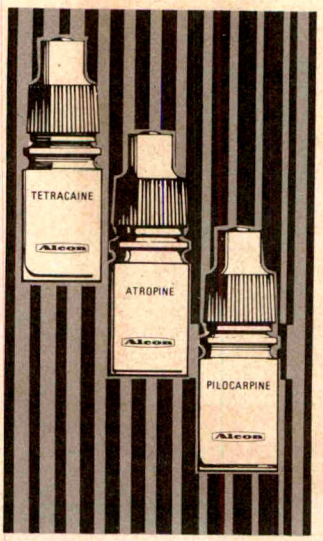




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  (1% Atropine Sulfate)
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Apply to conjuctiva at bedtime.

TO REDUCE CORNEAL EDEMA



Murocoll Methylcellulose
4000 cps 0.9%
with Sodium Chloride 5%

MUROCOLL PRODUCT NO. 4 / SUPPLIED 15cc and 30cc

A hypertonic solution of sodium chloride with methylcellulose. Preservatives - methylparaben and propylparaben.

TO REDUCE CORNEAL EDEMA: 1 or 2 drops in affected eye 3 times a day or as directed by the physician.

MURO preparations are available to all pharmacies and hospitals through their drug wholesaler.

Complete ophthalmologic formulary available on request.

Federal law prohibits dispensing without prescription.

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Severe ocular inflammation calls for potent therapy...

The basis for a rational choice between FML® (fluorometholone) and Pred Forte® (prednisolone acetate) 1%

When to use a potent steroid. If not treated promptly and effectively, ocular inflammation is at best painful and unsightly. At worst, it's potentially damaging to the patient's vision. The more severe the inflammatory condition, the greater the need for therapeutic potency. For example, FML and Pred Forte provide the high level of anti-inflammatory activity needed to effectively treat even the most severe steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe.

The basic rationale behind the use of potent ophthalmic steroids such as FML and Pred Forte is to maintain functional integrity of the eye. In general, as long as evidence of active inflammation persists, it may be hazardous to discontinue steroid therapy. Use of potent steroids may in fact help preserve the ocular structure.[1]

When not to use potent steroids. Despite their usefulness, there are times when potent steroids (and mild ones too, for that matter) should be used with extreme caution – or not at all. It is generally agreed that untreated purulent infections, most viral diseases and ocular fungal infestations should be considered as contraindications to the use of these agents.

Indications and methods of use. Either FML or Pred Forte may be used to treat moderately severe to severe steroid responsive inflammatory conditions such as iritis, uveitis, iridocyclitis, episcleritis and resistant ocular allergy. In addition, data[2] made available recently attest to the usefulness of FML in long-term treatment of inflammation following cataract removal and keratoplasty. The patient photos to the right demonstrate the effectiveness of both FML and Pred Forte in severe ocular inflammation.

The usual method of administering either FML or Pred Forte is to instill one or two drops into the conjunctival sac two to four times a day. But to provide maximum therapeutic effectiveness when the severity of the inflammation dictates, the dosage can be *safely* increased to two drops every hour during the first 24 to 48 hours

OSI Office Seminars IN Ophthalmology

FML® (fluorometholone) 0.1% Liquifilm® Sterile Ophthalmic Suspension

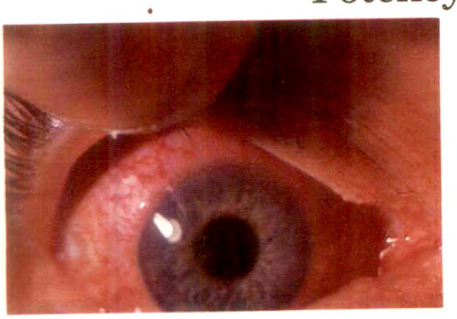
ACTIONS Inhibition of the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. Adrenocorticosteroids and their derivatives are capable of producing a rise in intraocular pressure. In clinical studies on patients' eyes treated with both dexamethasone and fluorometholone, fluorometholone demonstrated a lower propensity to increase intraocular pressure than did dexamethasone. **INDICATIONS** For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **CONTRAINDICATIONS** Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **WARNINGS** Steroid medication in the treatment of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by presence of steroid medication. Safety and effectiveness have not been demonstrated in children of the age group 2 years or below. Use In Pregnancy: Safety of the use of topical steroids during pregnancy has not been established. **PRECAUTIONS** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intraocular pressure should be checked frequently. **ADVERSE REACTIONS** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe. **DOSAGE AND ADMINISTRATION** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

FML®
fluorometholone)

Pred Forte®
(prednisolone acetate) 1%

FML vs Pred Forte: A choice. Both FML and Pred Forte work. FML has been shown to have less propensity than dexamethasone to raise IOP.[1] And recent animal data[2] indicate that Pred Forte exhibits maximal corneal penetration, through intact epithelium, compared to commonly used steroid phosphate and alcohol derivatives. So when potent anti-inflammatory activity is required and your clinical judgement anticipates something beyond short-term therapy, FML appears to be the drug of choice. But for severe disorders where safety is less of a concern, Pred Forte provides a potent alternative to FML.

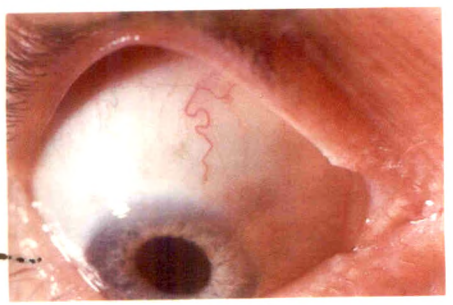
Potency you can see



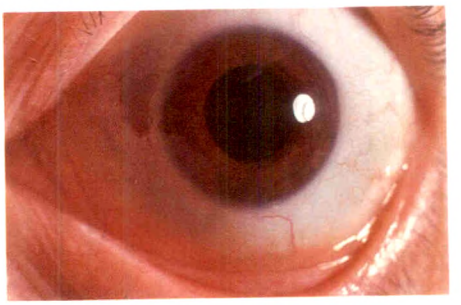
Patient CH. White male. Age 46. Acute episcleritis secondary to rheumatoid arthritis. Treatment started 2/24: FML one drop every hour for 48 hours then one drop every two hours for 36 hours then one drop every four hours thereafter.



Patient LV. White male. Age 57. Acute episcleritis. Treatment started 2/27: Pred Forte one drop every hour for 48 hours then one drop every two hours for 36 hours then one drop every four hours thereafter; warm compresses and scopolamine ointment twice daily.



Patient CH on 3/9. FML therapy stopped.



Patient LV on 3/12. Pred Forte therapy stopped.

References

1. Leopold, I.H. The steroid shield in ophthalmology, Trans Amer Acad Ophth & Oto 71:273–289, 1967.

2. Castroviejo, R. Data presented at 79th American Academy of Ophthalmology and Otolaryngology, Dallas, Oct. 1974.

3. Leibowitz, Howard M., Data presented at 79th American Academy of Ophthalmology and Otolaryngology, Dallas, Oct. 1974.

Photos by Dr. Ira Abrahamson, Cincinnati, Ohio

Pred Forte® (prednisolone acetate) 1% Sterile Ophthalmic Suspension

INDICATIONS For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **CONTRAINDICATIONS** Acute untreated purulent ocular infections, acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, ocular tuberculosis, and fungal diseases of the eye, and sensitivity to any components of the formulation. **WARNINGS** 1. In those diseases causing thinning of the cornea, perforation has been reported with the use of topical steroids. 2. Since PRED FORTE® contains no antimicrobial, if infection is present appropriate measures must be taken to counteract the organisms involved. 3. Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids. 4. Use of steroid medication in the presence of stromal herpes simplex requires caution and should be followed by frequent mandatory slit-lamp microscopy. 5. As fungal infections of the cornea have been reported coincidentally with long-term local steroid applications, fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use. 6. Use of topical corticosteroids may cause increased intraocular pressure in certain individuals. This may result in damage to the optic nerve with defects in the visual fields. It is advisable that the intraocular pressure be checked frequently. 7. Use in Pregnancy–Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. **PRECAUTIONS** Posterior subcapsular cataract formation has been reported after heavy or protracted use of topical ophthalmic corticosteroids. Patients with histories of herpes simplex keratitis should be treated with caution. **ADVERSE REACTIONS** Increased intraocular pressure, with optic nerve damage, defects in the visual fields. Also posterior subcapsular cataract formation, secondary ocular infections from fungi or viruses liberated from ocular tissues, and perforation of the globe when used in conditions where there is thinning of the cornea or sclera. Systemic side effects may occur with extensive use of steroids. **DOSAGE AND ADMINISTRATION** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

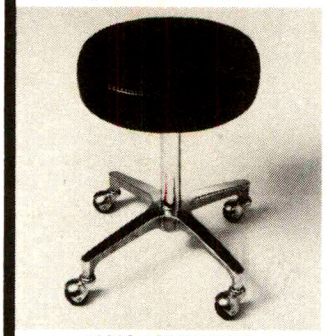
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#1010 SCREW TYPE

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SPECIFICATIONS AND DIMENSIONS:

MODELS 1020 and 1020B
Standard Height Adjustment — From 20" to 26½". Other height adjustments available. Standard cushioned backrest tilts automatically for custom comfort (Model 1020B and 1010B). Base — 19" Span (Standard) (See optional equipment below).

1020 WITHOUT BACKREST–$125.00
1020B WITH BACKREST–$150.00

MODEL 1010 and 1010B
Standard Height Adjustment from 19" to 27". Other height adjustments available. Base—19" Span (Standard) (See opt. equip. below).

1010 WITHOUT BACKREST–$75.00
1010B WITH BACKREST–$99.50

All stools available from low height of 17" upward to any height desired with a 6½" stroke. Any stool less than 17" low height will only have a 3½" height adjustment.

OPTIONAL EQUIPMENT AT EXTRA COST

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Special colors available at slight additional charge.

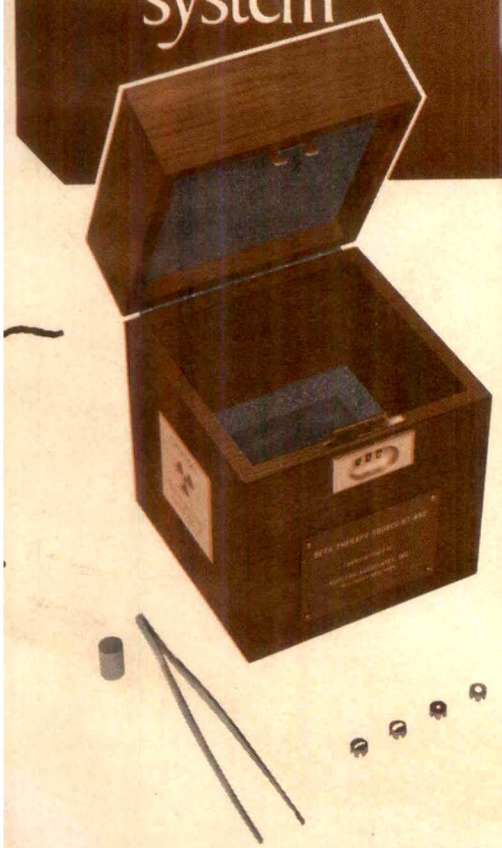
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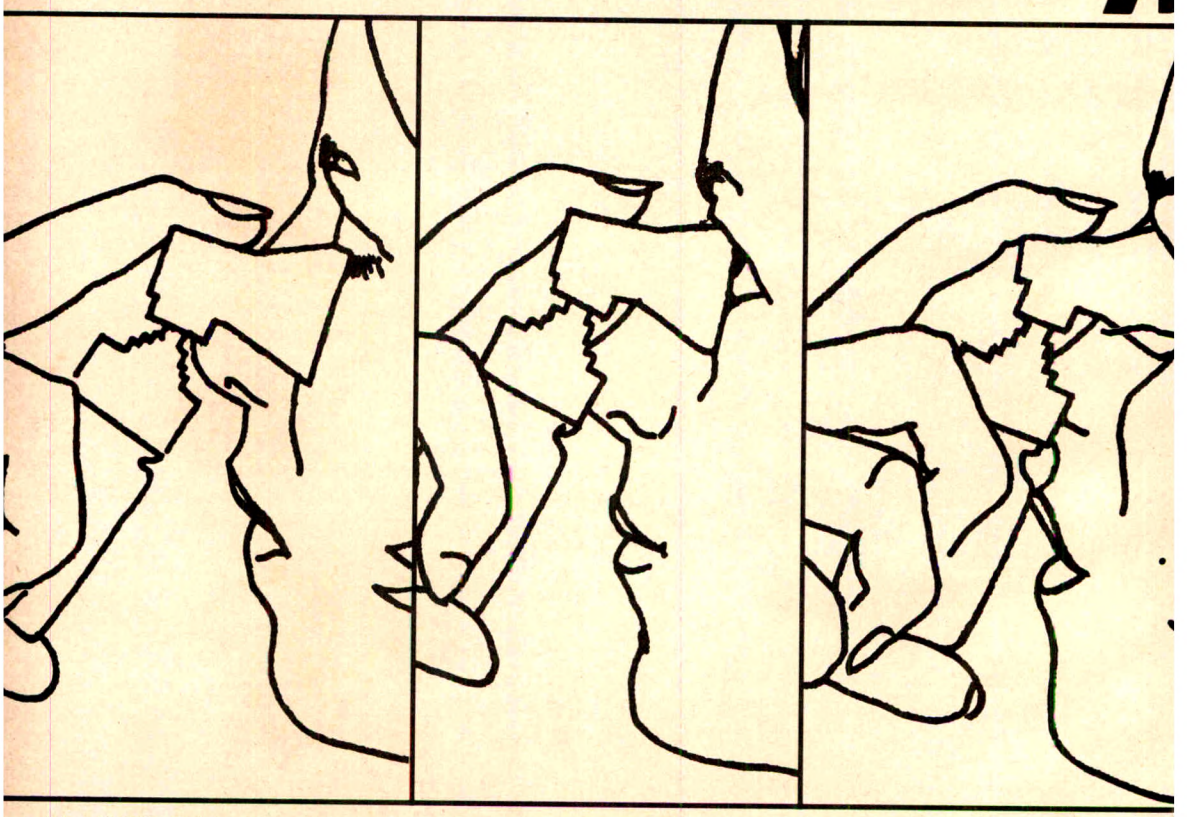
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3365 Tree Court Industrial Blvd., St. Louis, Mo. 63122

Average applanation tonometry readings of 22 glaucoma patients treated first with pilocarpine drops—and then with pilocarpine mist (MISTURA® P Pilocarpine HCl).*

TONOMETRY READINGS (mm/Hg)					
On drops prior to treatment with mist		Approximately 1 month after start of treatment with mist		Two to four months after start of treatment with mist	
R. eye	L. eye	R. eye	L. eye	R. eye	L. eye
17.9	18.2	18.5	19.0	18.2	18.6
12-22	14-24	13-24	16-28	12-26	12-24

*Drug Delivery Systems for Topical Ophthalmic Medication, by G. Peter Halberg, M.D., FACS, Stephen E. Kelly, M.D., Michael Morrone, M.S., Annals of Ophthalmology, September, 1975.

Tonometrically,



Hold MISTURA between finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

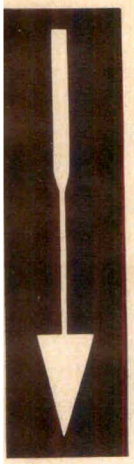
Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.

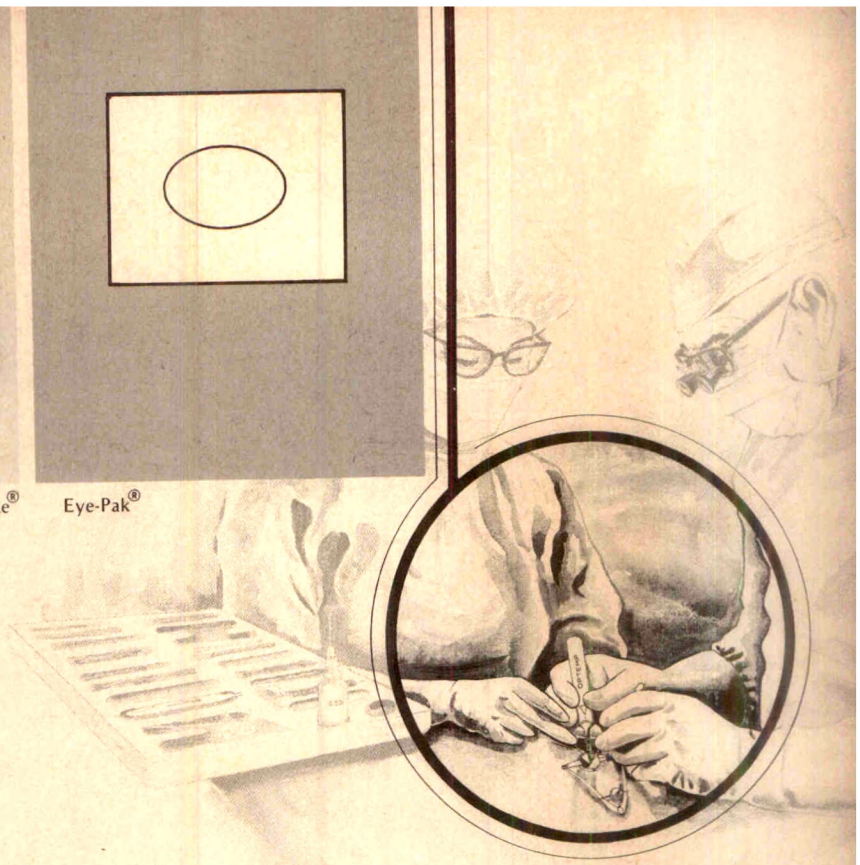


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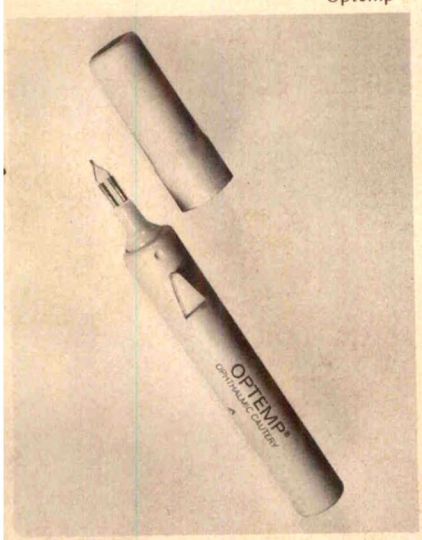
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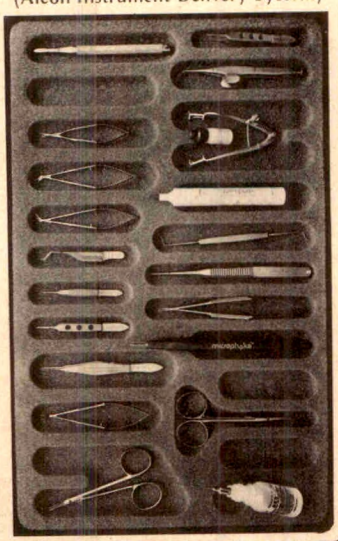
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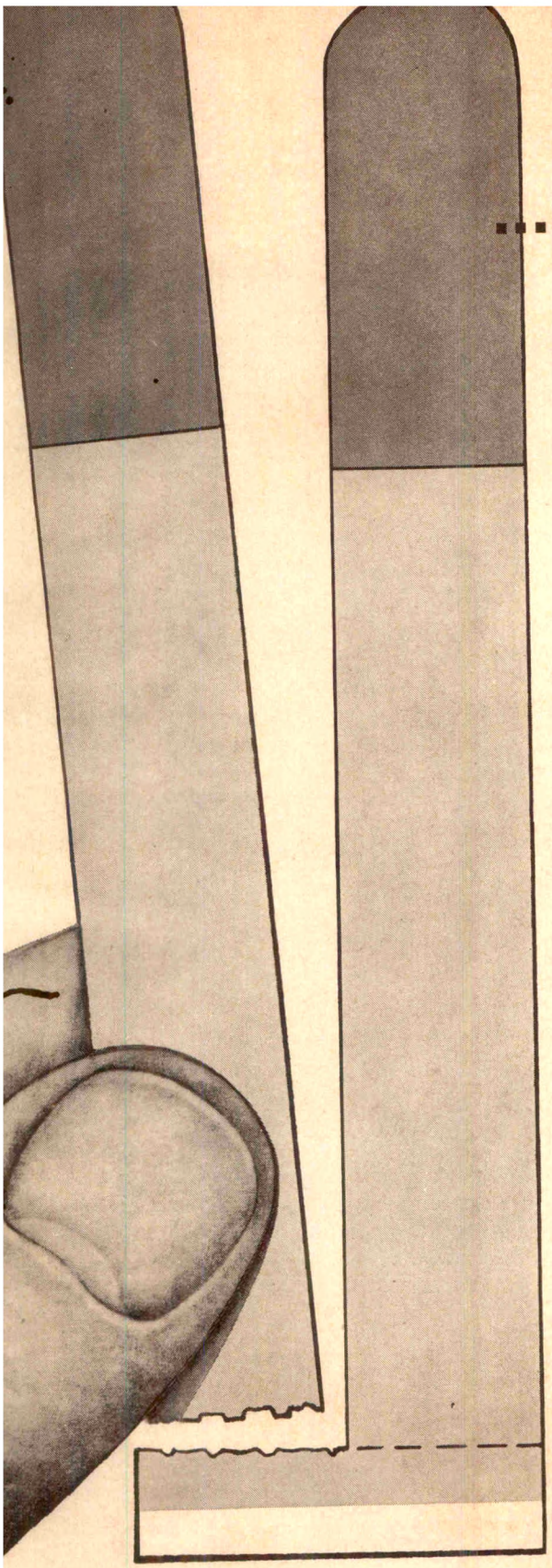
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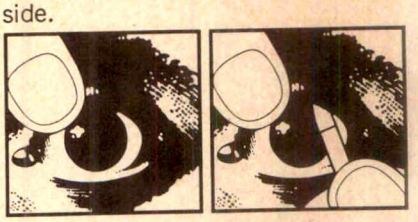
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Alpha Chymar®
(STERILE CHYMOTRYPSIN)
FOR OPHTHALMIC USE

DESCRIPTION Each vial of ALPHA CHYMAR® (Sterile Chymotrypsin) contains 750 N.F. Units of chymotrypsin. A vial containing 10 ml. of Sodium Chloride Injection U.S.P. is provided as ALPHA CHYMAR® DILUENT.

ACTION Dissolution of zonular fibers attached to the lens by proteolytic enzymatic action.

INDICATION ALPHA CHYMAR® (Sterile Chymotrypsin) is indicated for enzymatic zonulysis for intracapsular lens extraction.

CONTRAINDICATIONS High vitreous pressure and a gaping incisional wound, congenital cataracts, and patients under 20 years because of probable lens-vitreous adhesion not responsive to alpha-chymotrypsin lysis.

PRECAUTIONS Instruments and syringes employed with preparation and use of solution must be free of enzyme inactivating alcohol and other chemicals. Excessive heat, such as autoclaving, inactivates the enzyme. Do not use the solution if it is cloudy or contains a precipitate.

ADVERSE REACTIONS Transient increases in intra-ocular pressure, moderate uveitis, corneal edema and striation have been reported. Delayed healing of incisions have been reported but has not been confirmed.

DOSAGE AND ADMINISTRATION Using aseptic technique transfer 5 ml. of the ALPHA CHYMAR® DILUENT to the vial containing ALPHA CHYMAR®. The resulting solution contains 150 N.F. Units per ml. which is equivalent to a 1:5000 dilution of alpha-chymotrypsin. The balance of the ALPHA CHYMAR® DILUENT may be used to flush out the enzyme solution after the zonules are digested.

NOTE: After the operation discard unused portion, including the diluent.

CAUTION: Excessive heat may alter alpha-chymotrypsin—do not autoclave the powder or reconstituted solution. Do not use if the reconstituted solution is cloudy or contains a precipitate.

SUGGESTED PROCEDURE

(1) Dilate pupils with a suitable mydriatic.
(2) Either local or general anesthesia may be used.
(3) Make corneoscleral or corneoscleral-conjunctival incision.
(4) Irrigate the posterior chamber (under the iris) with about 1-2 ml. of ALPHA CHYMAR® (Sterile Chymotrypsin) solution.
(5) Perform peripheral or complete iridectomy or iridotomy.
(6) Place sutures if not preplaced. (Chromic or silk recommended).
(7) Wait two to four minutes then irrigate with at least 2 ml. of the unused portion of the Diluent, or Sodium Chloride Injection, U.S.P.
NOTE: If the zonules are still intact, irrigate with an additional 1-2 ml. of ALPHA CHYMAR® solution. This irrigation may be made through the iridectomy opening. After two to four minutes, irrigate with about 2 ml. of Diluent or Sodium Chloride Injection U.S.P. and attempt lens delivery.
(8) Extract with erisophake or forceps—tumbling delivery may be used if desired. Forceps should be used with caution to avoid possible dislocation of the lens posteriorly.
(9) The pupils may be contracted with a suitable miotic.

A 1:5000 (150 N.F. Units/ml.) dilution has been widely used. With experience, however, the surgeon may adjust the concentration and volume to obtain the optimal effect.

HOW SUPPLIED ALPHA CHYMAR® is available in packages containing one vial of lyophilized ALPHA CHYMAR® (Sterile Chymotrypsin) and one vial of ALPHA CHYMAR® DILUENT.

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(sterile chymotrypsin)

Alpha Chymar® was the first and is the number one product in use for zonulolysis.

Alpha Chymar® has relieved "that moment of anxiety for the cataract surgeon when he meets up with a tough zonula."*

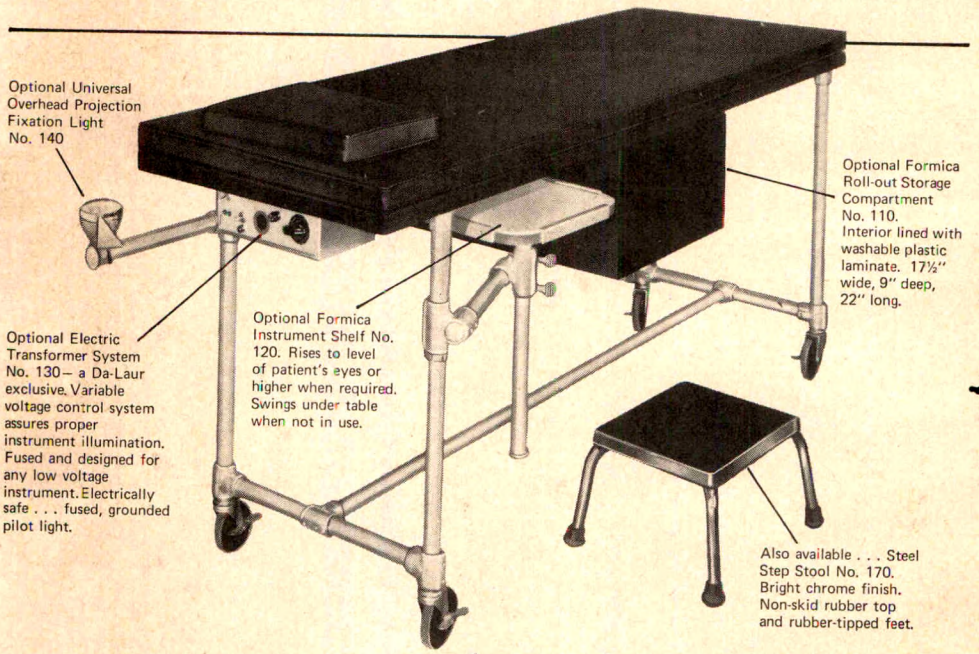
*Thorpe, H. E., Am. J. Op[illegible]

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Blephamide® for Blepharitis.

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Ophthalmologists see conjunctivitis about 5 times as often as blepharitis.

For that reason, we want to make sure the name Blephamide doesn't mislead you. True, it's the leading drop for the treatment of blepharitis, but it's just as effective in patients with non-purulent conjunctivitis.

And why shouldn't it be. The Blephamide formula was designed to treat this frequently mixed condition. Prednisolone acetate in microfine particles acts to reduce inflammation while the sodium sulfacetamide attacks the infection. In Blephamide drops, phenylephrine decongests engorged blood vessels quickly. And the soothing Liquifilm® vehicle provides longer drug-contact time than does an aqueous solution.

For truly 'round the clock treatment, Blephamide S.O.P. sterile ophthalmic ointment provides convenient once-a-night dosage and long-lasting lubrication.

Together, Blephamide drops and ointment offer your patients effective treatment for blepharitis and conjunctivitis and conjunctivitis and conjunctivitis and . . .

BLEPHAMIDE S.O.P. STERILE OPHTHALMIC OINTMENT

BLEPHAMIDE LIQUIFILM OPHTHALMIC SUSPENSION

INDICATIONS: Based on a review of this drug by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Nonpurulent blepharitis and blepharoconjunctivitis (seborrheal, staphylococcal, allergic); nonpurulent conjunctivitis (allergic and bacterial).
Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Acute herpes simplex (dendritic keratitis), purulent untreated infections, vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, ocular tuberculosis and fungal diseases of the eye.

WARNINGS: 1) In diseases due to microorganisms, infection may be masked, enhanced or activated by the steroid. 2) Extended use may cause increased intraocular pressure in susceptible individuals. It is advisable that the intraocular pressure be checked frequently. 3) In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. 4) Use with caution in patients with known or suspected sensitivity to sulfonamides — if sensitivity or other untoward reactions occur, discontinue medication. 5) Should be used with caution in the presence of narrow angle glaucoma. 6) Reports in the literature indicate that posterior subcapsular lenticular opacities have been reported to occur after heavy or protracted use of topical ophthalmic corticosteroids. USE IN PREGNANCY: Safety of the use of topical steroids during pregnancy has not been established.

PRECAUTIONS: Ophthalmic ointments may retard corneal healing.

Blephamide® Liquifilm®

(sodium sulfacetamide 10.0%, prednisolone acetate 0.2%, phenylephrine HCl 0.12%)

OPHTHALMIC SUSPENSION

Blephamide® S.O.P.®

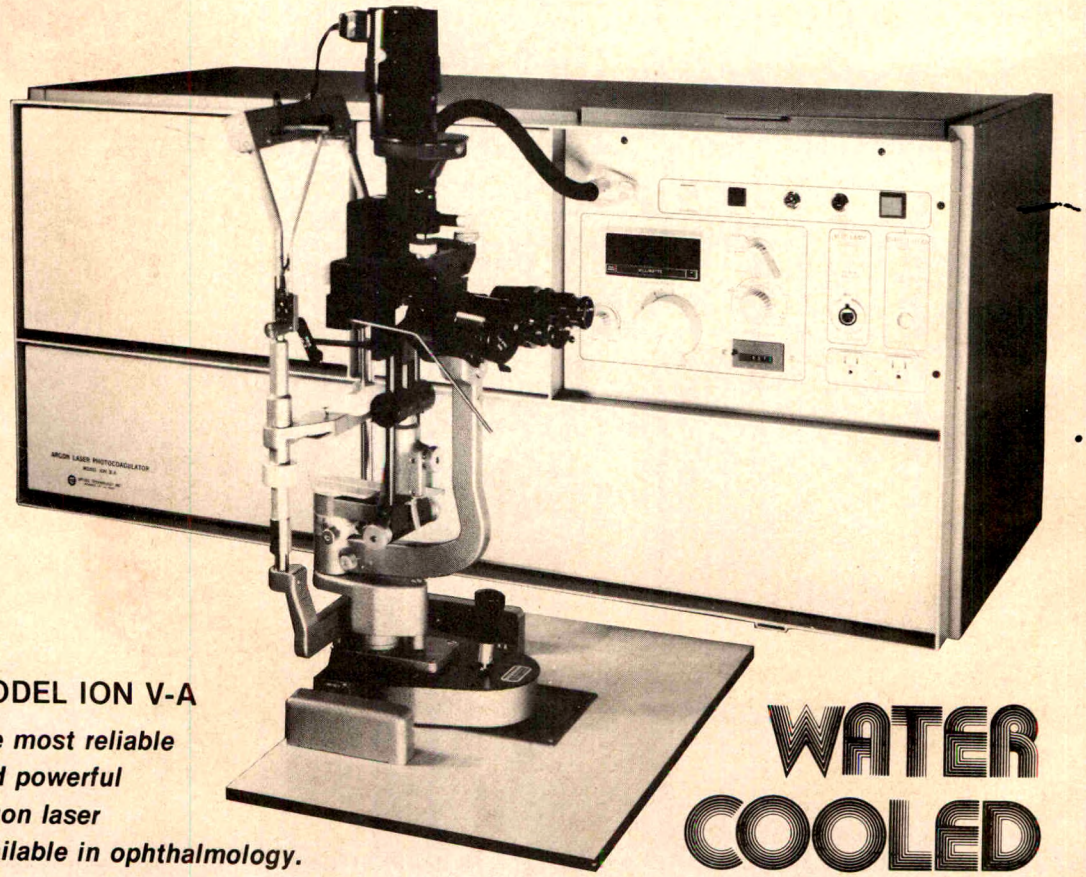
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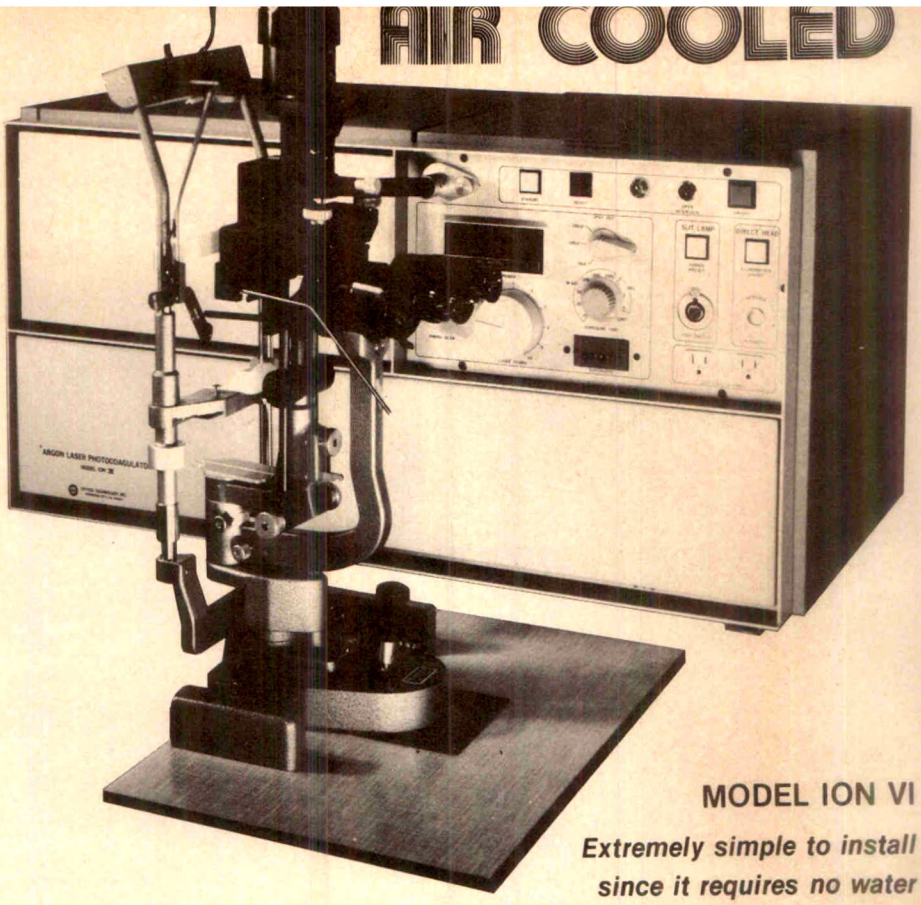


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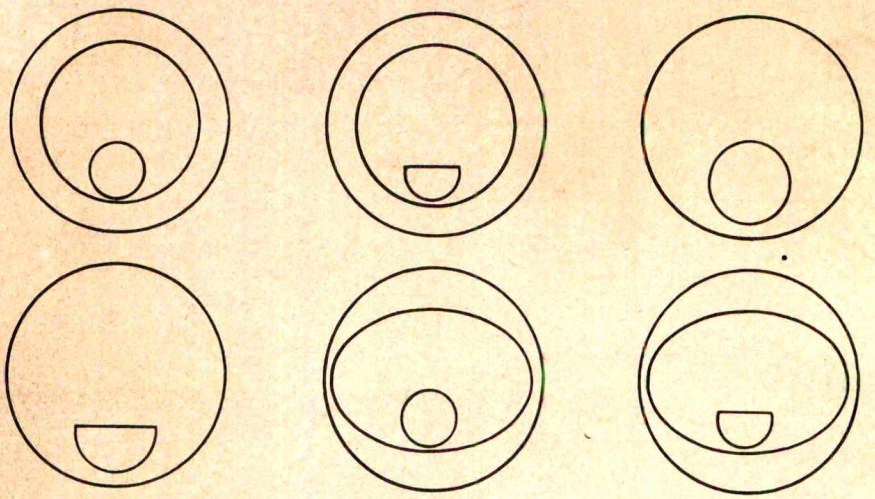
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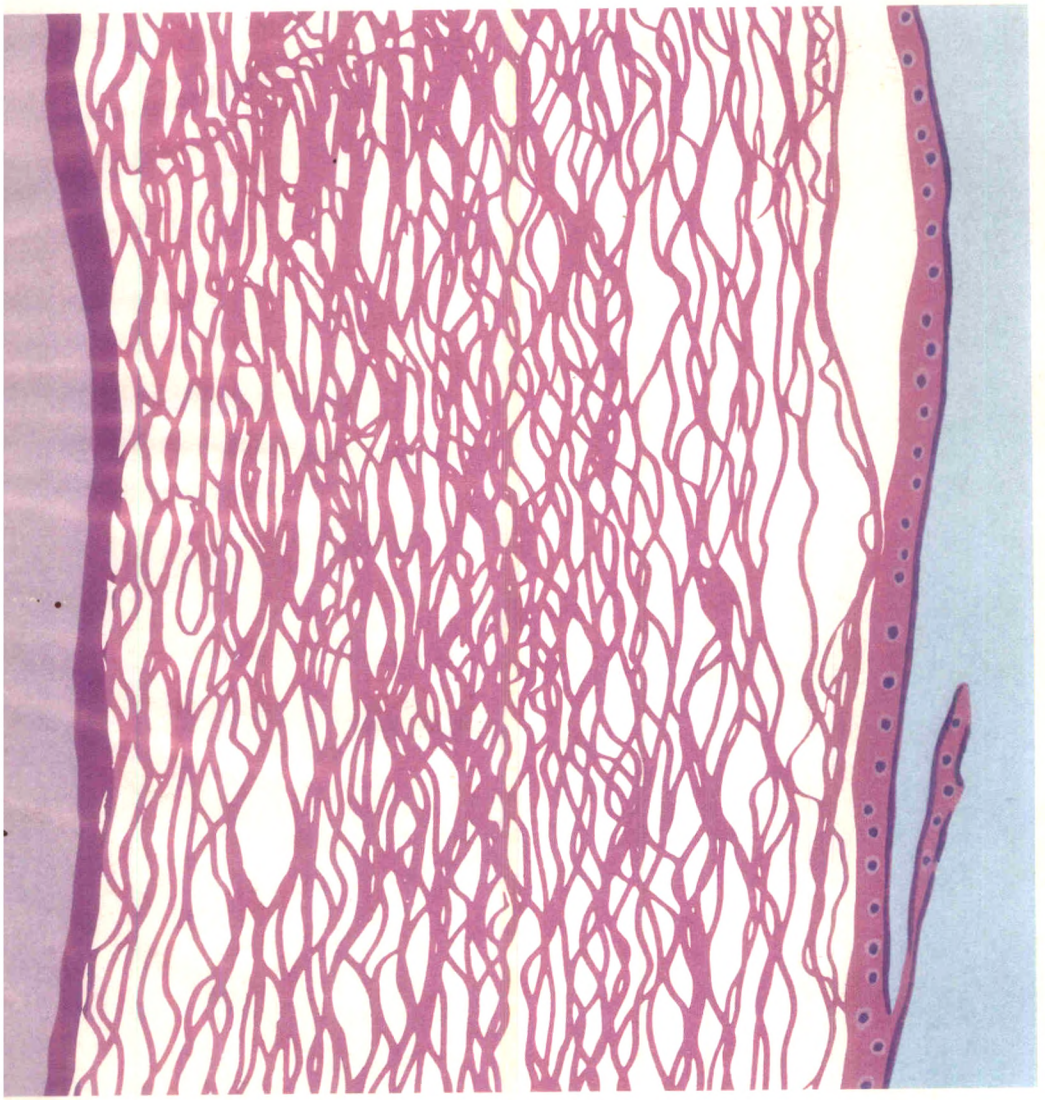
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CONTACT LENS

Advances into Ocular Therapy



Bullous Keratopathy

Clinical experience*:
77.3% of patients demonstrate pain relief*

Clinical studies conducted by 21 ophthalmologists in hospitals and private clinical practices confirm SOFLENS® (polymacon) Contact Lens effectiveness in relieving the pain of bullous keratopathy. Of 348 patients, 269 or 77.3% experienced relief from pain following application of the lens. Seventy-nine patients or 22.7% were unsuccessful in wearing the lens. The primary reasons given for lack of success were poor tolerance, discomfort, no change in symptoms, poor visual acuity, or poor fit.

Therapeutic Advances:

Now SOFLENS Contact Lenses are recommended for relief of the painful symptoms of bullous keratopathy. Although all lens series (B, F, J, N, C, and T) may be utilized as transparent barriers to protect the cornea from eyelid friction, the new plano T series is particularly well suited for this therapeutic application.

Because the T lens is large (14.7mm), relatively thin (.18mm), and fits comfortably on most eyes, it should be the lens of first choice.

Therapeutic Advantages:

The SOFLENS Contact Lens is biologically and chemically inert, dimensionally stable, and reliable. These qualities which make the lens a lens of choice in vision correction, when indicated, now provide an effective modality to aid the physician in meeting his therapeutic goals. Placement of the lens generally results in rapid pain relief for the patient.

Therapeutic Convenience:

Medication with preservatives may be used in the usual dosage regimens when indicated. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens. Since all SOFLENS Contact Lens series and powers are available for the treatment of bullous keratopathy, vision correction may also be possible.

SOFLENS Contact Lenses are contraindicated in the presence of any active, untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

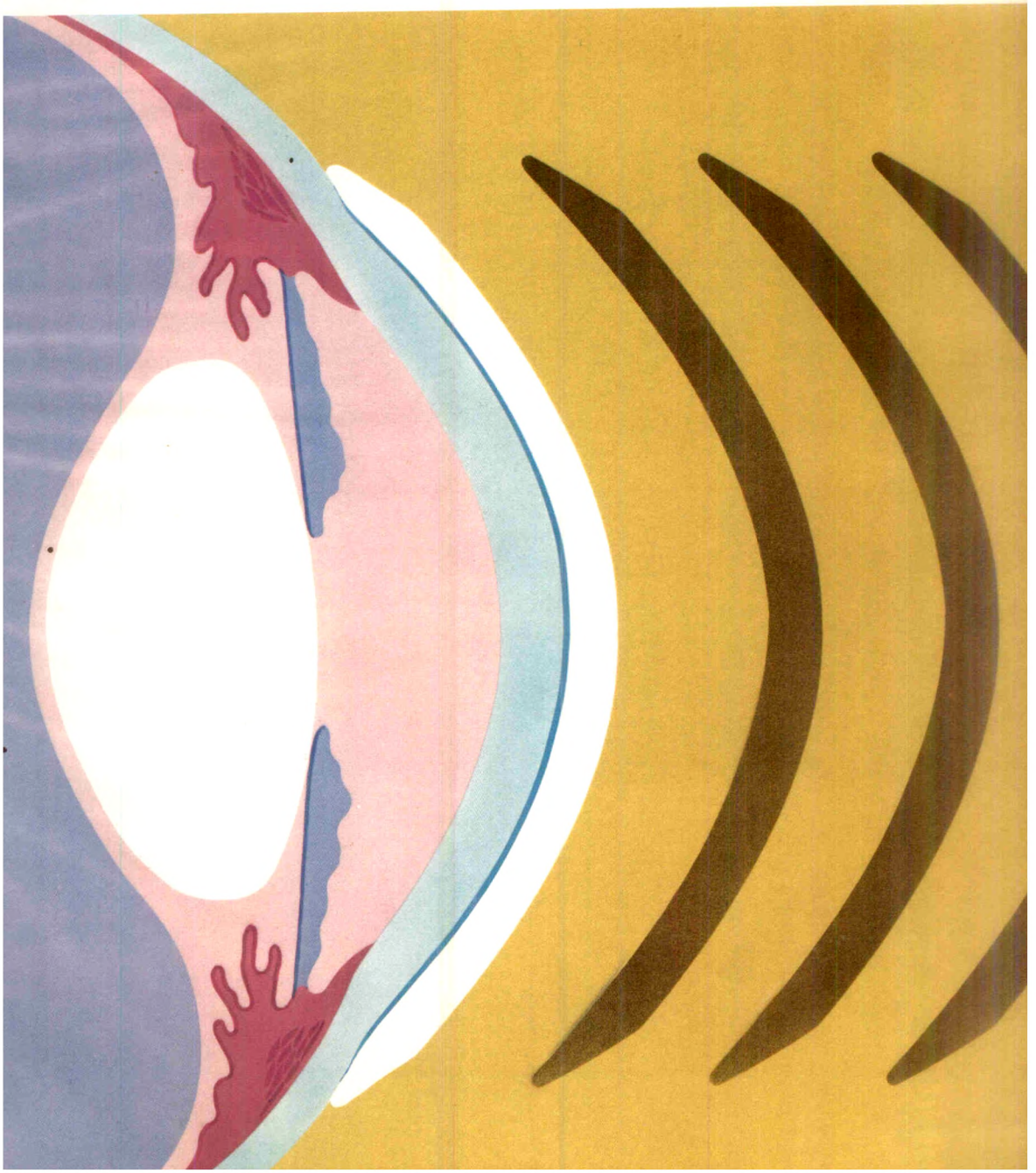
SOFLENS Contact Lenses are easily applied by the physician. Because of flexibility and thin edges of the lenses, most patients adjust to them quickly. While the patient's pain is controlled, the physician gains time to consider other therapeutic procedures. Thus, the SOFLENS Contact Lens preserves future therapeutic options.

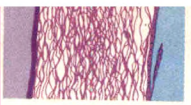
*Data on file at Bausch & Lomb Incorporated. Available on request.

For Bullous Keratopathy you can prescribe with confidence

soflens®
(polymacon)
CONTACT LENS

For therapeutic application, choose the new plano T series or... the B, F, J, N, and C SOFLENS Contact Lens series.





(polymacon) CONTACT LENS

THERAPEUTIC USE

DESCRIPTION: The SOFLENS® (polymacon) Contact Lens is a hemispherical flexible shell which covers the cornea and may cover a portion of the adjacent sclera. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The material has a refractive index of 1.43 and the lens has a visible light transmittance of more than 97%.

ACTIONS: In its hydrated state a SOFLENS Contact Lens is soft and pliable. When placed on the human cornea, the hydrated SOFLENS Contact Lens acts as a refracting medium to compensate spherical ametropias and as a pain reliever by providing a well tolerated barrier between the exposed corneal nerves and the lids.

INDICATIONS: SOFLENS® (polymacon) Contact Lenses may be useful in the treatment and management of painful bullous keratopathy.

CONTRAINDICATIONS: SOFLENS Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

WARNINGS: Patients should be instructed to consult their physician if the eye becomes uncomfortable or irritated. If undue delay is anticipated, the lens should be removed immediately and stored in normal saline.

SOFLENS Contact Lenses must not be used in combination with solutions commonly used for cleaning, wetting and storage of hard contact lenses as these will produce severe corneal irritation.

The patient should be instructed to use only eyedrops prescribed by the physician when the lens is on the eye.

Medication with preservatives may be used when indicated in the usual dosage regimens. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens.

Deposits, which frequently occur on the lens with continuous wear, may cause discomfort and necessitate replacement as often as every two or three months.

SOFLENS® (polymacon) Contact Lenses should not be used in the presence of noxious and irritating vapors. Safety in pregnancy has not been substantiated. Insufficient lacrimal secretion or hypoesthesia may be restricting factors to the wearing of soft contact lenses.

Malfunction and rusting of the metal interior of the Aseptor®–Patient Unit as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure.

Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses.

PRECAUTIONS: Placement and Removal–SOFLENS® (polymacon) Contact Lenses should be applied and removed only by the physician. However, all patients should be instructed in the techniques of placing and removing a lens, so they can do so should it become necessary.

When the SOFLENS Contact Lens is used for the treatment of painful bullous keratopathy, it is to be worn continuously, for 24 hours a day, following the initial application. The patient should be followed closely during the initial stages of treatment. The lens should be comfortable and the pain of bullous keratopathy should be relieved almost immediately. If the lens is not comfortable and pain persists, another lens should be tried for appropriate fit.

Daily placement and removal of the lens by the patient may be permitted. However, if daily removal increases the risk of additional damage to the already compromised corneal epithelium and when the degree of pain relief is significant during the time the lens is worn, continuous wear should be employed.

Storage–SOFLENS® (polymacon) Contact Lenses must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in normal saline solution until it returns to its soft, pliable state which may take as long as forty minutes.

Fresh normal saline must be prepared for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The one ounce squeeze bottle is intended for preparation of normal saline only. As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected.

Hygiene–Hands must be washed, rinsed thoroughly, and dried wi towel before handling the lenses.

Cosmetics, lotions, soaps, and creams must not come in contact wi since eye irritation may result. If hair spray is used while the lens worn, the eyes must be kept closed until the hair spray has settled.

Handling–A SOFLENS® (polymacon) Contact Lens may be damaged tearing if care is not exercised during placement on or removal fr replacing or removing it from the carrying case or in the cleaning pro must be placed very carefully in the carrying case to avoid damaging the lenses.

Disinfecting–Fresh normal saline must be prepared daily. After remo eye, the SOFLENS® (polymacon) Contact Lens must be irrigated wit rubbed gently to remove mucus and film from the lens' surface. The c must be emptied and refilled with fresh normal saline solution disinfecting the lenses.

The SOFLENS Carrying Case should be washed at least once a w water and then rinsed thoroughly with distilled water. Soap or otl should never be used to clean the carrying case.

Disinfecting with the SOFLENS Aseptor®–Patient Unit is nece microorganisms.

If a SOFLENS Aseptor is not available, the lenses may be disinfecte them in their carrying case in a pan of water for 15 minutes. When method of disinfection is used, the lenses can be damaged if the boi allowed to completely evaporate.

The carrying case must always be tightly closed before disinfectin leakage of the saline from the case and subsequent dehydration of

Fluorescein–Never use fluorescein while the patient is wearing because the lenses will become discolored. Whenever fluorescein is the eyes with sterile normal saline solution and wait at least one replacing the lenses. Earlier replacement may cause the lenses to abs fluorescein.

ADVERSE REACTIONS: Infiltrates, neovascularization, and corneal been reported.

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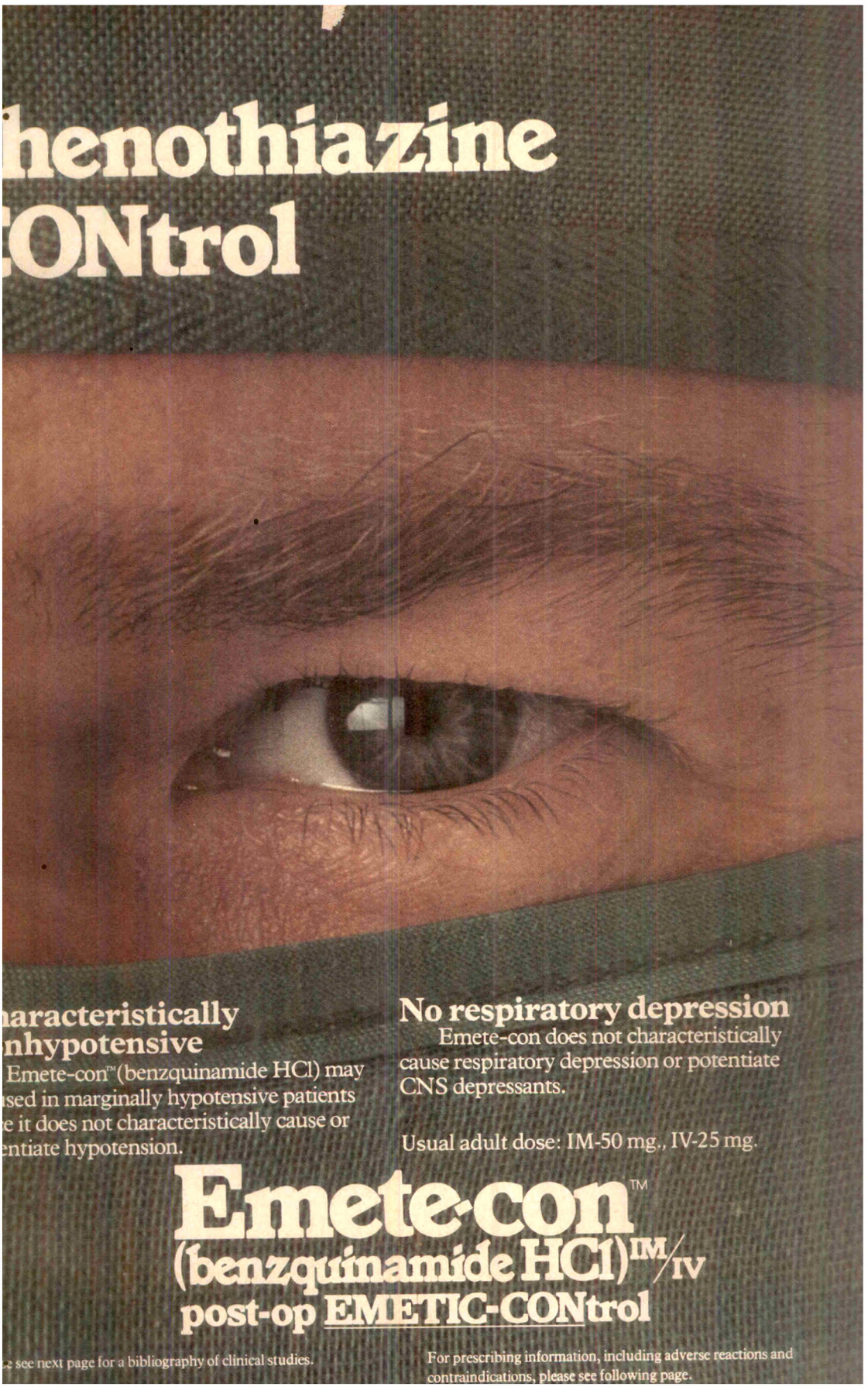
The SOFLENS Care Kit is available for lens disinfecting, cleaning a consisting of the following:

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SOFLENS Aseptor®–Patient Unit	Cat. #1
SOFLENS Squeeze Bottle	Cat. #1
SOFLENS Salt Tablets	Cat. #1
SOFLENS Patient Instruction Book	Cat. #1

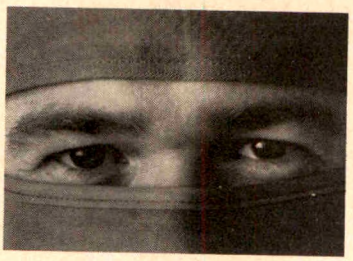
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SOFLENS DIVISION
Rochester, N.Y. 14602


henothiazine
ONtrol
aracteristically
nhypotensive
Emete-con™(benzquinamide HCl) may
sed in marginally hypotensive patients
e it does not characteristically cause or
ntiate hypotension.
No respiratory depression
Emete-con does not characteristically cause respiratory depression or potentiate CNS depressants.
Usual adult dose: IM-50 mg., IV-25 mg.
Emete-con™
(benzquinamide HCl)™/IV
post-op EMETIC-CONtrol
see next page for a bibliography of clinical studies.
For prescribing information, including adverse reactions and contraindications, please see following page.

Emete-con™
(benzquinamide HCl) IM/IV
post-op EMETIC-CONtrol



PRESCRIBING INFORMATION
Emete-con™ (benzquinamide hydrochloride)
For Intramuscular and Intravenous Use

Description. Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide hydrochloride) is N, N-diethyl-1,3,4,6,7, 11b-hexahydro-2-hydroxy-9, 10-dimethoxy-2H-benzo [a] quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5$. HCl and the molecular weight is 441.

Emete-con for injection contains benzquinamide hydrochloride equivalent to 50 mg/vial of benzquinamide and 0.45 mg/vial of citric acid. When reconstituted with 2.2 ml of proper diluent, each vial yields 2 ml of a solution containing benzquinamide hydrochloride equivalent to 25 mg/ml of benzquinamide and 0.02% citric acid. When reconstituted this product maintains its potency for 14 days at room temperature.

Actions. Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con (benzquinamide hydrochloride) should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected—*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg–1.0 mg/kg))

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-co quinamide hydrochloride) should be inje within the mass of a larger muscle. Th area should be used only if well develo jections should not be made into the lower thirds of the upper arm. Aspiration of th should be carried out to avoid inadverte vascular injection.

Therapeutic blood levels and demonstra emetic activity appear within fifteen mi intramuscular administration. When the of therapy is the prevention of nausea an ing, intramuscular administration is recon at least fifteen minutes prior to emergen anesthesia.

Intravenous: 25 mg (0.2 mg/kg–0.4 m a single dose) administered slowly (1 ml to 1 minute). Subsequent doses should intramuscularly.

The intravenous route of administratio be restricted to patients without cardio disease (See WARNINGS). If it is nece use Emete-con intravenously in elderly o tated patients, benzquinamide should be tered cautiously and the lower dose recommended.

This preparation must be initially reco with 2.2 ml of Sterile Water for Injectio teriostatic Water for Injection with benzyl or with methylparaben and propylparabe procedure yields 2 ml of a solution equiv 25 mg benzquinamide/ml. which maint potency for 14 days at room temperature

Overdosage. *Manifestations:* On the basis animal toxicology studies, gross Emete-co dosage in humans might be expected to itself as a combination of Central Nervous stimulant and depressant effects. This spe is derived from experimental studies in intravenous doses of benzquinamide, at le times the human therapeutic dose, were a tered to dogs.

Treatment: There is no specific antid Emete-con overdosage. General supportiv sures should be instituted, as indicated. A may be helpful. Although there has been n experience with dialysis, it is not likely t value, since benzquinamide is extensively to plasma protein.

How Supplied. Emete-con for IM/IV use i able in a vial containing benzquinamid equivalent to 50 mg of benzquinamide in p of 10 vials.

Caution. Federal law prohibits dispensing prescription.

ROERIG Pfize
A division of Pfizer Pharmaceutic
New York, New York 10017

Bibliography

Zauder, H. L., et al.: Prophylaxis of Postoperative Emesis, Scientific Exhibit presented at 122nd Annual Convention of the A.M.A., June 23-27, 1973.

Lutz, H., and Immich, H.: Antiemetic effect of benzquinamide in postoperative vomiting. Curr. Ther. Res. 14:178, April, 1972.

Finn, H., et. al.: Antiemetic efficacy of benzquinamide. N.Y. J. Med. 71:61, March 15, 1971. Larrauri, R. M.: Benzquinamide parenteral for the treatment of post-operative nausea and vomiting. Curr. Ther. Res. 11:65, March, 1969.

Steen, S. N. and Yates, M.: The Effects of Benzquinamide and Prochlorperazine, Separately and Combined, on the Human Respiratory Center. Anesthesiology 36:519, May, 1972.

Emete-con™
(benzquinamide HCl) IM/I
post-op EMETIC-CONtrol

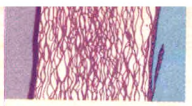
Each vial contains benzquinamide hydrochloride equivalent to 50 mg. of benzquinamide with 0.45 mg. of citric acid.

For Bullous Keratopathy you can prescribe with confidence

soflens®
(polymacon)
CONTACT LENS

For therapeutic application, choose the new plano T series or... the B, F, J, N, and C SOFLENS Contact Lens series.





(polymacon) CONTACT LENS

THERAPEUTIC USE

DESCRIPTION: The SOFLENS® (polymacon) Contact Lens is a hemispherical flexible shell which covers the cornea and may cover a portion of the adjacent sclera. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The material has a refractive index of 1.43 and the lens has a visible light transmittance of more than 97%.

ACTIONS: In its hydrated state a SOFLENS Contact Lens is soft and pliable. When placed on the human cornea, the hydrated SOFLENS Contact Lens acts as a refracting medium to compensate spherical ametropias and as a pain reliever by providing a well tolerated barrier between the exposed corneal nerves and the lids.

INDICATIONS: SOFLENS® (polymacon) Contact Lenses may be useful in the treatment and management of painful bullous keratopathy.

CONTRAINDICATIONS: SOFLENS Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

WARNINGS: Patients should be instructed to consult their physician if the eye becomes uncomfortable or irritated. If undue delay is anticipated, the lens should be removed immediately and stored in normal saline.

SOFLENS Contact Lenses must not be used in combination with solutions commonly used for cleaning, wetting and storage of hard contact lenses as these will produce severe corneal irritation.

The patient should be instructed to use only eyedrops prescribed by the physician when the lens is on the eye.

Medication with preservatives may be used when indicated in the usual dosage regimens. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens.

Deposits, which frequently occur on the lens with continuous wear, may cause discomfort and necessitate replacement as often as every two or three months.

SOFLENS® (polymacon) Contact Lenses should not be used in the presence of noxious and irritating vapors. Safety in pregnancy has not been substantiated. Insufficient lacrimal secretion or hypoesthesia may be restricting factors to the wearing of soft contact lenses.

Malfunction and rusting of the metal interior of the Aseptor®–Patient Unit as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure.

Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses.

PRECAUTIONS: Placement and Removal–SOFLENS® (polymacon) Contact Lenses should be applied and removed only by the physician. However, all patients should be instructed in the techniques of placing and removing a lens, so they can do so should it become necessary.

When the SOFLENS Contact Lens is used for the treatment of painful bullous keratopathy, it is to be worn continuously, for 24 hours a day, following the initial application. The patient should be followed closely during the initial stages of treatment. The lens should be comfortable and the pain of bullous keratopathy should be relieved almost immediately. If the lens is not comfortable and pain persists, another lens should be tried for appropriate fit.

Daily placement and removal of the lens by the patient may be permitted. However, if daily removal increases the risk of additional damage to the already compromised corneal epithelium and when the degree of pain relief is significant during the time the lens is worn, continuous wear should be employed.

Storage–SOFLENS® (polymacon) Contact Lenses must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in normal saline solution until it returns to its soft, pliable state which may take as long as forty minutes.

Fresh normal saline must be prepared for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The one ounce squeeze bottle is intended for preparation of normal saline only. As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected.

Hygiene–Hands must be washed, rinsed thoroughly, and dried wit towel before handling the lenses.

Cosmetics, lotions, soaps, and creams must not come in contact wi since eye irritation may result. If hair spray is used while the lens worn, the eyes must be kept closed until the hair spray has settled.

Handling–A SOFLENS® (polymacon) Contact Lens may be damaged tearing if care is not exercised during placement on or removal fr replacing or removing it from the carrying case or in the cleaning pro must be placed very carefully in the carrying case to avoid damaging the lenses.

Disinfecting–Fresh normal saline must be prepared daily. After remo eye, the SOFLENS® (polymacon) Contact Lens must be irrigated wit rubbed gently to remove mucus and film from the lens' surface. The c must be emptied and refilled with fresh normal saline solution disinfecting the lenses.

The SOFLENS Carrying Case should be washed at least once a w water and then rinsed thoroughly with distilled water. Soap or otl should never be used to clean the carrying case.

Disinfecting with the SOFLENS Aseptor®–Patient Unit is nece microorganisms.

If a SOFLENS Aseptor is not available, the lenses may be disinfecte them in their carrying case in a pan of water for 15 minutes. When method of disinfection is used, the lenses can be damaged if the boi allowed to completely evaporate.

The carrying case must always be tightly closed before disinfectin leakage of the saline from the case and subsequent dehydration of

Fluorescein–Never use fluorescein while the patient is wearing because the lenses will become discolored. Whenever fluorescein is the eyes with sterile normal saline solution and wait at least one replacing the lenses. Earlier replacement may cause the lenses to abs fluorescein.

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SOFLENS Patient Instruction Book	Cat. #1

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Will be introduced to the professio
at the A.A.O.O. meeting, Dalla
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can't play
any
position.



Accommodative esotropia may prevent a child from developing the skills necessary for competitive sports. Lack of binocular single vision may affect school work as well as play...and negative cosmetic effects may alter peer relationships.

Phospholine Iodide (echothiophate iodide) may be able to change the lineup.

Diagnosis... To help determine if there is an accommodative basis for the esotropia, one drop of PHOSPHOLINE IODIDE 0.125% may be instilled daily in each eye, prior to retiring, for two or three weeks.

Treatment... If there is a significant accommodative factor present, the continued use of PHOSPHOLINE IODIDE alone is often sufficient for treatment, as long as the drug is well tolerated. PHOSPHOLINE IODIDE acts by altering the accommodative convergence/accommodation relationship in a favorable way, so that near vision is obtained with less accommodative effort, and fusion can be maintained.

If surgery is necessary, postoperative use of PHOSPHOLINE IODIDE may help correct a residual deviation.

Phospholine Iodide®

(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)

in the diagnosis and treatment of accommodative esotropia

BRIEF SUMMARY
(For full prescribing information, see package circular.)

PHOSPHOLINE IODIDE®
(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.

Indications: 1. Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia—Concomitant esotropias with a significant accommodative component.

Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.

Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or in the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.

Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.

Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.

Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.

How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

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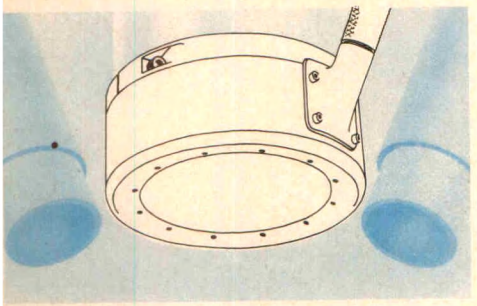
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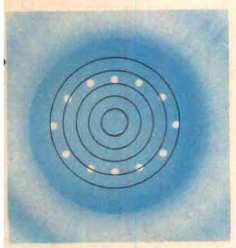
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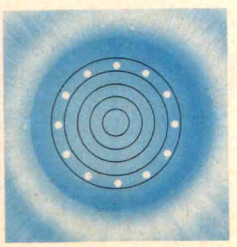
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The Weck (Troutman) Operating Keratometer identifies the problem now...during surgery

when excessive suture tension, resulting in corneal astigmatism can most easily be corrected.







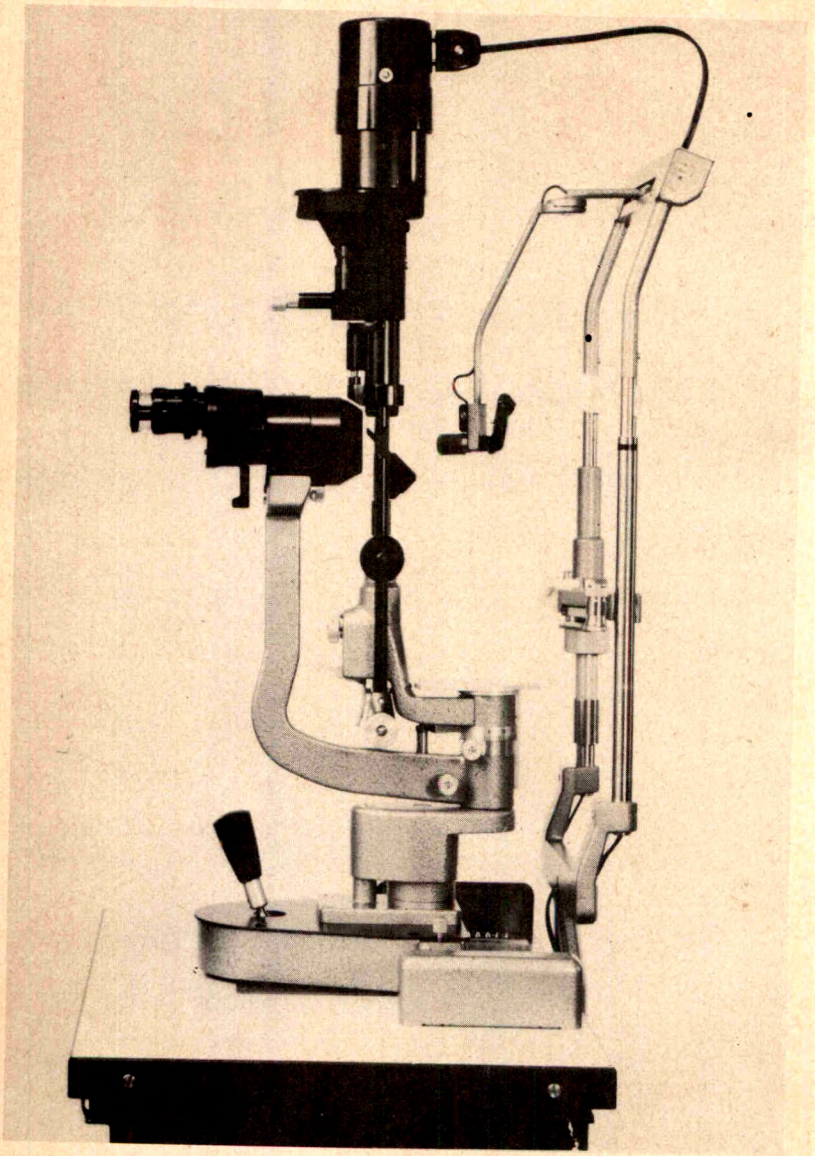
The unit contains a series of **fiber-optic** powered pinpoints of light. These are arranged circumferentially about the operating microscope objective lens, and are reflected from cornea to surgeon. A **circular** pattern identifies to him that the cornea is anastigmatic. An **elliptical** pattern will result when the cornea is steepened along one meridian for example by too tight a suture or mal-apposition of the wound.

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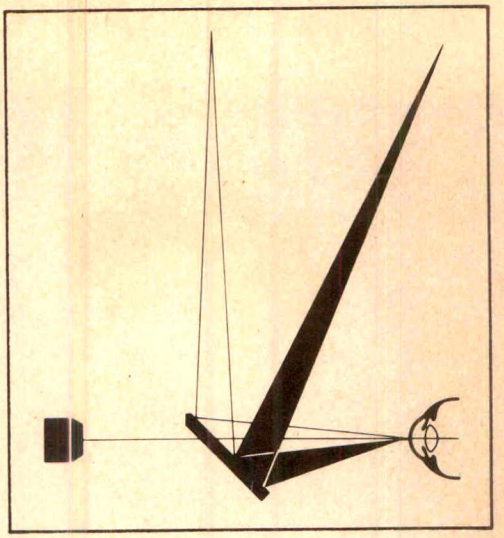
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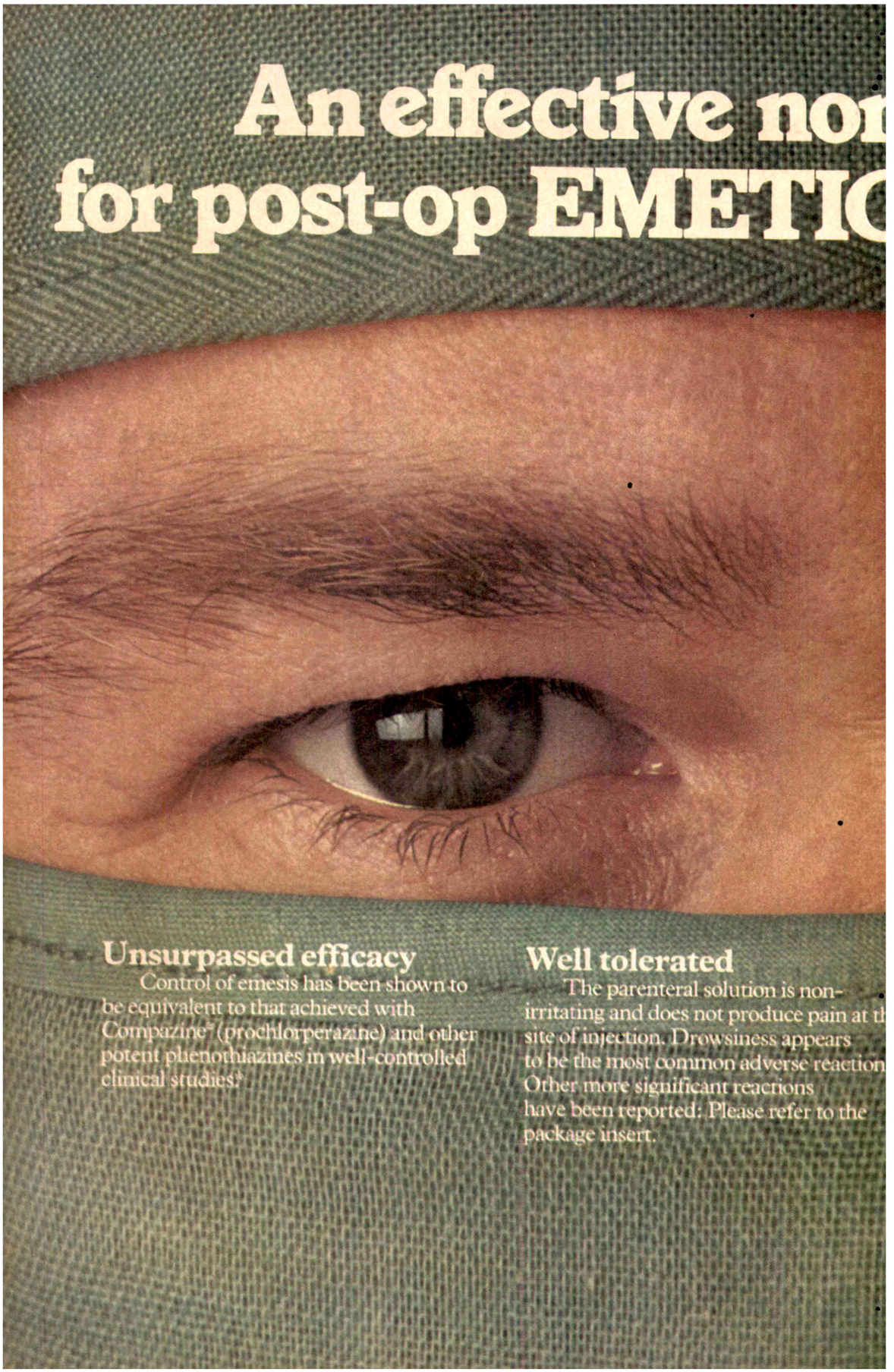
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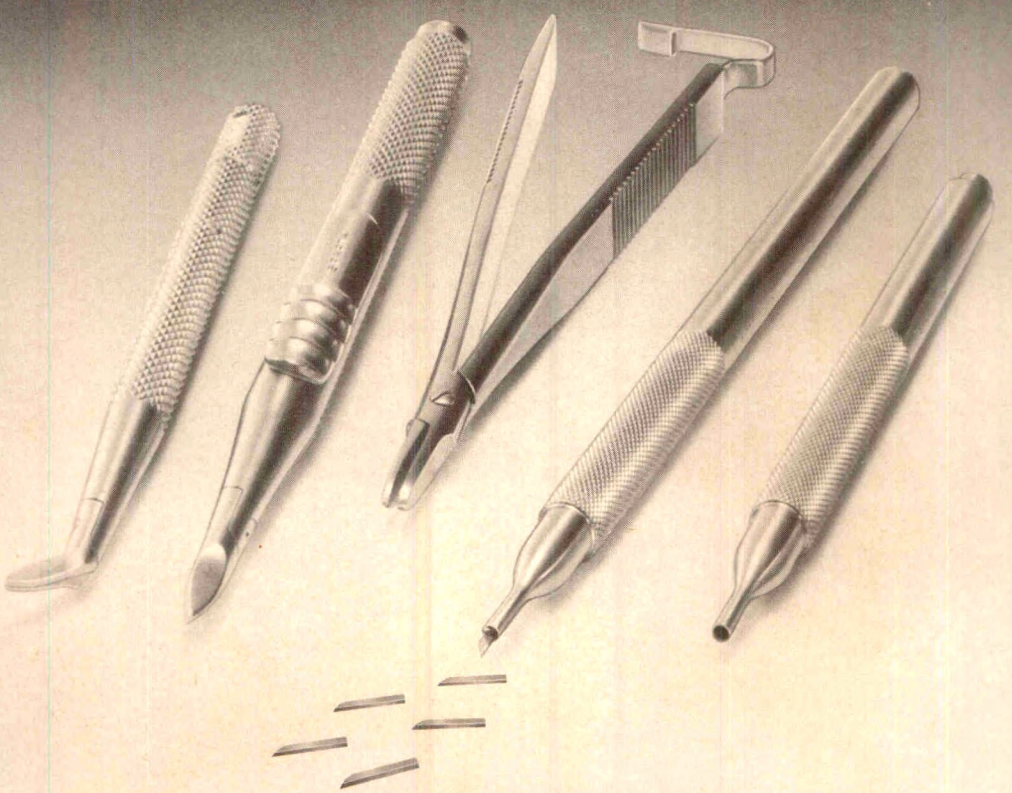
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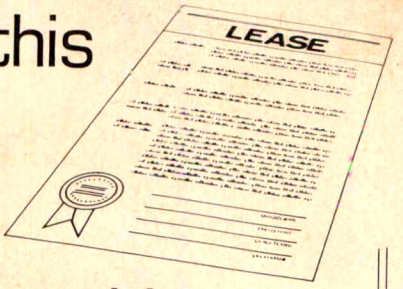
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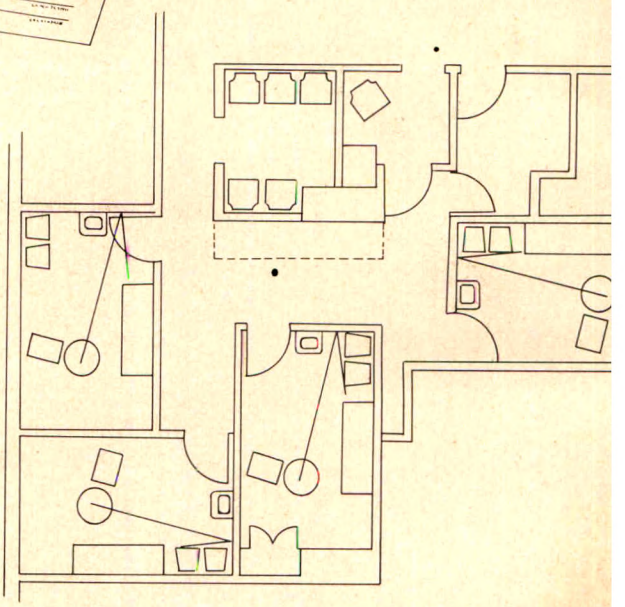
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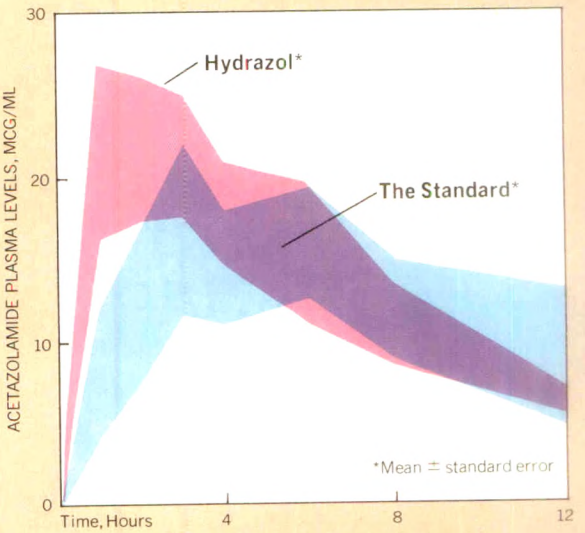
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(acetazolamide) 250 mg

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Caution: Federal law prohibits dispensing without prescription.

Description: Each Hydrazol (acetazolamide) tablet contains 250 mg acetazolamide.

Indications: For adjunctive treatment of chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Contraindications: Hydrazol (acetazolamide) therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, suprarenal gland failure, and hyperchloremic acidosis. Long-term administration of acetazolamide is contraindicated in patients with chronic noncongestive angle closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intraocular pressure.

Warnings: Studies of acetazolamide in rats and mice have demonstrated teratogenic and embryocidal effects at doses in excess of 10 times those recommended in human beings. There is no evidence of these effects in human beings. However, acetazolamide should not be used in pregnancy, especially during the first trimester, unless the benefits to be expected outweigh these potential adverse effects.

Precautions: Increasing the dosage above one gram usually does not increase the desired effect and may increase the incidence of drowsiness and/or paresthesia.

Adverse reactions: Adverse reactions common to all sulfonamide derivatives may occur; fever, rash, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, and agranulocytosis. Precaution is advised for early detection of such reactions and the drug should be discontinued and appropriate therapy instituted.

Adverse reactions noted during short term therapy have been minimal. They include: paresthesias (particularly a "tingling" feeling in the extremities), some loss of appetite, polyuria, and occasional instances of drowsiness and confusion.

During long-term therapy, an acidotic state may occasionally supervene. This can usually be corrected by the administration of bicarbonate.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuance of the medication.

Other occasional adverse reactions include: urticaria melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, and convulsions.

Dosage and administration: Hydrazol (acetazolamide) should be used as an adjunct to the usual therapy for glaucoma. The dosage employed in the treatment of *chronic simple (open-angle) glaucoma* ranges from 250 mg to 1 gram of acetazolamide per 24 hours, usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 1 gram per 24 hours does not produce an increased effect. In all cases, the dosage should be adjusted with careful individual attention both to symptomatology and ocular tension. Continuous supervision by a physician is advisable.

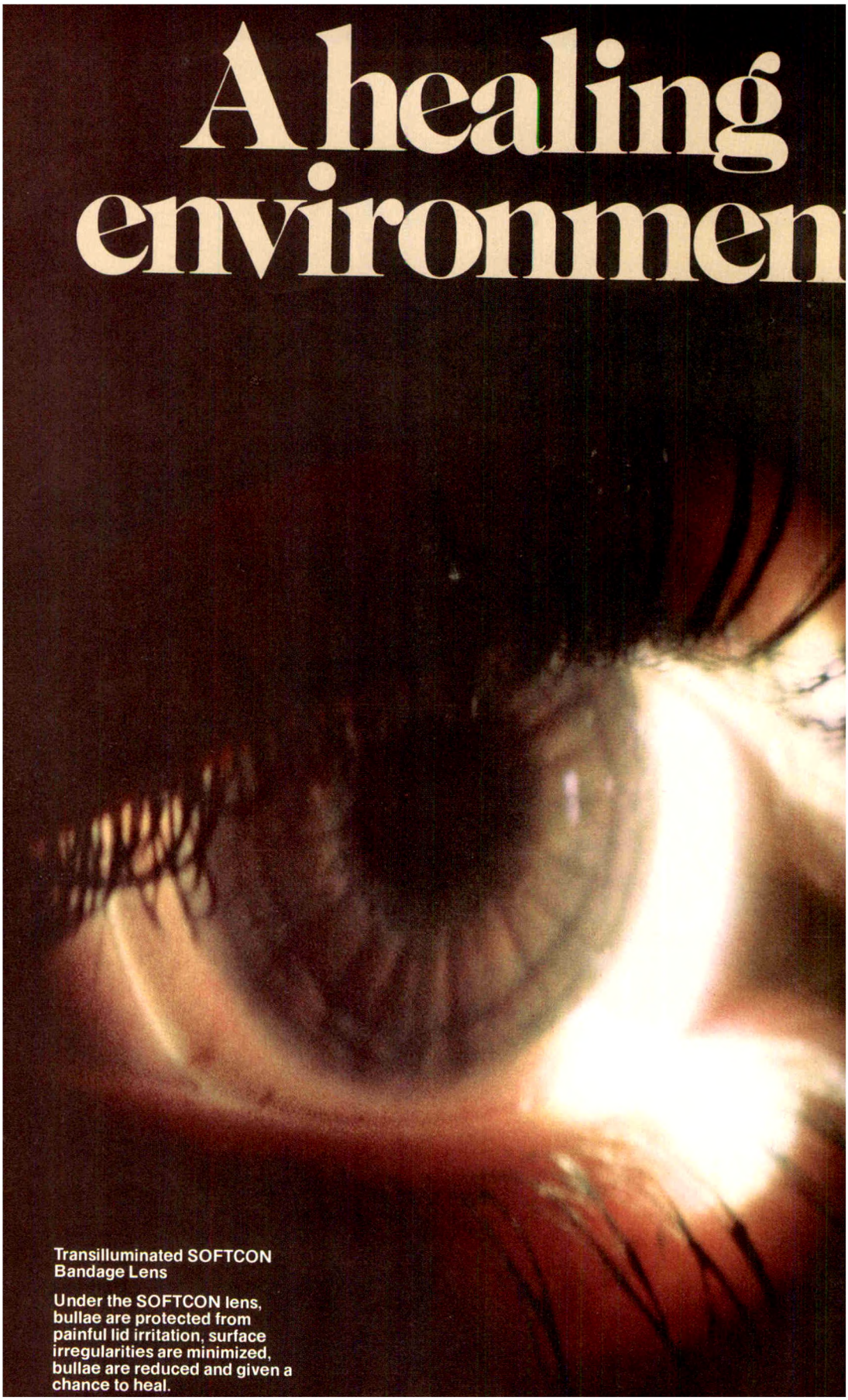
In the treatment of secondary glaucoma and in the preoperative treatment of some cases of *acute congestive (closed-angle) glaucoma*, the preferred dosage is 250 mg every four hours, although some cases have responded to 250 mg twice daily on short-term therapy. In some acute cases, it may be more satisfactory to administer an initial dose of 500 mg followed by 125 or 250 mg every 4 hours, depending on the individual case. A complementary effect has been noted when acetazolamide has been used in conjunction with miotics and mydriatics as the case demanded.

Note: The dosage recommendations for glaucoma differ considerably from those for other indications for acetazolamide, since treatment of glaucoma is not dependent upon carbonic anhydrase in the kidney.

How supplied: 250 mg round, yellow, quarter-scored tablets; coded "SP 250." (NDC 0346-0250-51) bottles of 100.

Full information is available on request.

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Transilluminated SOFTCON Bandage Lens

Under the SOFTCON lens, bullae are protected from painful lid irritation, surface irregularities are minimized, bullae are reduced and given a chance to heal.

Softcon®
(vifilcon A)
BANDAGE LENS
for the treatment of bullous keratopathy

A protective cover that can bring immediate and complete relief of pain

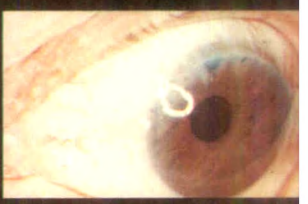
Until now, the pain of bullous keratopathy was often a virtual mandate for surgery. Now the SOFTCON Bandage Lens offers the patient round-the-clock pain relief and the physician a welcome opportunity to watch and wait. Edema may be so well controlled with the SOFTCON lens and hypertonic saline, that other measures never become necessary. In any case, an interim period of SOFTCON lens wear won't compromise future alternatives. In a study of 419 eyes with bullous keratopathy, the SOFTCON lens gave complete pain relief in 74% of cases and partial relief in 20%[1]

Distinct physical properties that enhance corneal metabolism

The SOFTCON lens is gel-like and virtually nonirritating, yet holds the curvature necessary for optical stability. The hydrophylic SOFTCON lens is about 55% water, equilibrates with the tear layer, and is permeable to oxygen and carbon dioxide. In a study of 465 eyes with bullous keratopathy, corneal status improved (by slit lamp evaluation) during SOFTCON lens wear in 66%, was unchanged in 30%, and worsened in only 3%[1]

A chance to preserve and even improve visual acuity during therapy

Before SOFTCON, treatment for severe corneal edema usually meant loss or limitation of existing visual acuity. A study of SOFTCON lens wear in 364 eyes with bullous keratopathy showed that visual acuity *improved significantly* in 33%, remained unchanged in 63%, and declined in only 4%[1]



Aphakic Fuchs' dystrophy. Note irregular reflex although cornea appears grossly clear. Acuity 20/160.



After almost 2 years of continuous SOFTCON bandage lens wear. 5% hypertonic saline solution b.i.d. Acuity 20/25 with overspectacles.

See next page for full product information

Softcon® (vifilcon A)

BANDAGE LENS

for bullous keratopathy



DESCRIPTION The SOFTCON (vifilcon A) corneal bandage lens is a semispherical flexible shell which covers the cornea and the adjacent sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, N.F. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON bandage lens may be useful in the treatment of bullous keratopathy to aid corneal healing, to relieve pain, to reduce corneal edema and, in selected cases, to improve vision.

CONTRAINDICATIONS Presence of any active infection of the eye.

WARNINGS The SOFTCON (vifilcon A) lens must be stored aseptically only in Lensrins™ NP. Use of other solutions, drops or cleaners may result in irritation or injury to the eye.

Patients must be instructed to consult their physician immediately if the eye becomes uncomfortable or irritated.

The lens must not be used in combination with solutions commonly used for cleansing, wetting and storage of conventional hard acrylic contact lenses, or with over-the-counter eye drops or medications. These solutions or medications may cause serious damage to the cornea when used with the corneal bandage lens. Cosmetics and hair sprays must not be allowed to come in contact with the lens. Patients should be warned accordingly. Safety in pregnancy has not been substantiated.

PRECAUTIONS Active eye infections should be appropriately treated before the insertion of the SOFTCON (vifilcon A) bandage lens.

Medications necessary to treat the disease condition should be used with caution, under close supervision. Hypertonic saline drops have been used concurrently without adverse effects. Quaternary ammonium compounds and other preservatives may cause ocular irritation. Other agents, epinephrine and fluorescein, for example, will cause discoloration of the lens.

Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Rarely a lens may adhere to an eye as a result of wearing a hypotonic lens. If a lens adheres for any reason, apply Lensrins NP and wait until the lens moves freely before removing it.

Lenses exposed to the air will dehydrate and become brittle. If this occurs, the lens should be soaked in Lensrins NP for one hour.

ADVERSE REACTIONS The following adverse reactions have been reported in patients using this lens for bullous keratopathy: corneal ulcer, ocular inflammation, ocular pain, hyperemia, keratoconjunctivitis, candida keratitis, neovascularization, excessive tearing and conjunctival injection.

Pain relief and improved corneal status in most patients; untoward experiences in very few

IN A STUDY OF 493 EYES (461 PATIENTS) WITH BULLOUS KERATOPATHY[1]:

Final wearing status

Lens wear continued	65%
Lens therapy completed	23%
Lens wear terminated	9%
Not stated	3%

Untoward experience during lens therapy

No	72%	Yes	28%

Type of untoward experience

Lost	24
Torn	18
Discolored	14
Uncomfortable	46
Deposit on lens	24
Not stated	5

DOSAGE AND ADMINISTRATION

Cleaning and Disinfecting Procedures

If the lens requires cleaning, it should be removed and cleaned by the physician by gently rubbing both sides of the lens between the fingers with a drop or two of Lensrins NP, followed by a rinse with lukewarm Lensrins NP. Any lens removed from the eye should be disinfected before being reapplied to the eye. The lens should be transferred to the glass vial supplie three-quarters full with Lensrins stoppered with a silicone rubber The vial is then closed with an alu tear seal, crimped with a crimping then boiled for at least fifteen mi either a boiling water bath or offi lizer. Allow the lens to cool before ing from the vial and insertion onto

Insertion and Removal Lenses be applied and removed only by th cian. All patients should be instru the technique of removing a lens this become necessary.

Fitting and Wearing Schedule may be fitted with lenses in re powers ranging from high (−25.00 D) to high plus (+25.0 0.50 diopter steps. These lenses recommended for use in cases tropia to correct visual acuity.

The SOFTCON (vifilcon A) banda is to be worn continuously, for 24 day, following initial application. should be followed closely durin stages of treatment. The lens sh comfortable and the pain of bullo topathy should be relieved. If the not comfortable and pain persists, lens should be tried for appropria

Patients should be examined peri for proper fit of the lens. A healing may change in geometric relat between the eye and the lens. Intol and discomfort experienced durin ing can usually be eliminated by the eye with a different lens. It is n narily necessary to remove the le the patient's eye at each follow-u The lens can be examined on the e a slit lamp.

HOW SUPPLIED Each SOF (vifilcon A) lens is supplied sterile in vial containing sodium chloride s USP. The label shows base curve eter, refractive power in diopte thickness.

The following are the commo dimensions available:

Base Curves (mm of radius)	7.8 8.1 8.4 8.7	Overall Chord Diameters (m	

For lens cleaning or disinfecting, lowing materials are available:

Lensrins NP; type I glass vials, 5 c cone rubber stoppers; aluminum crimping tool (available directly fr West Co., Phoenixville, Penna 19 Fermpress H 207).

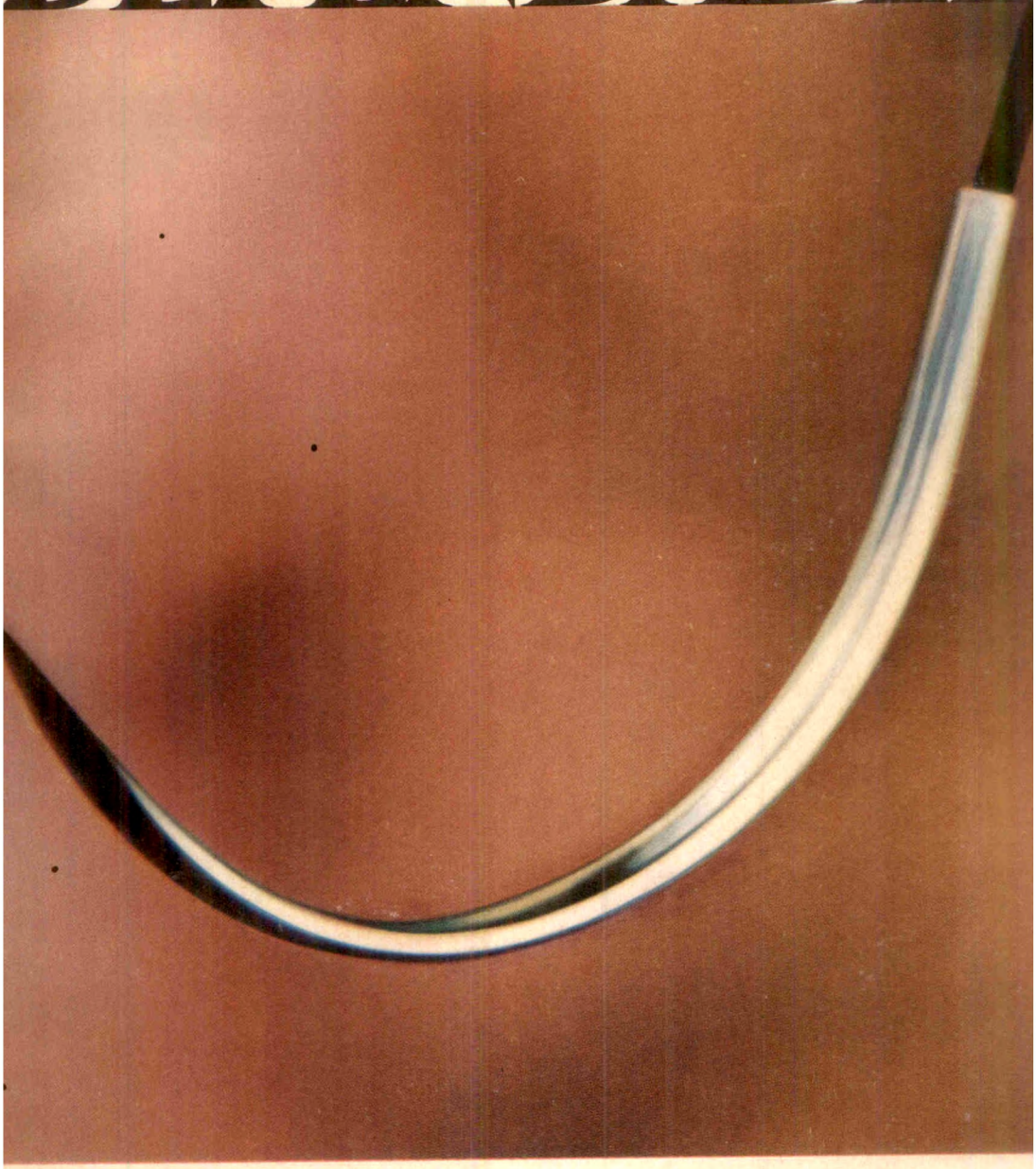
CAUTION: Federal Law Prohibi pensing Without A Prescription.

Reference: 1. Data on file, So Products, Div., Warner-Lambert Co

Softcon Products
Div., Warner-Lambert Company
Morris Plains, N.J. 07950

For further information on any in the Softcon Products line, wr Softcon Products Professional ices Dept., 201 Tabor Road, M Plains, New Jersey 07950.

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Dependability is in your hands with
ETHICON* premium quality stainless steel needles.

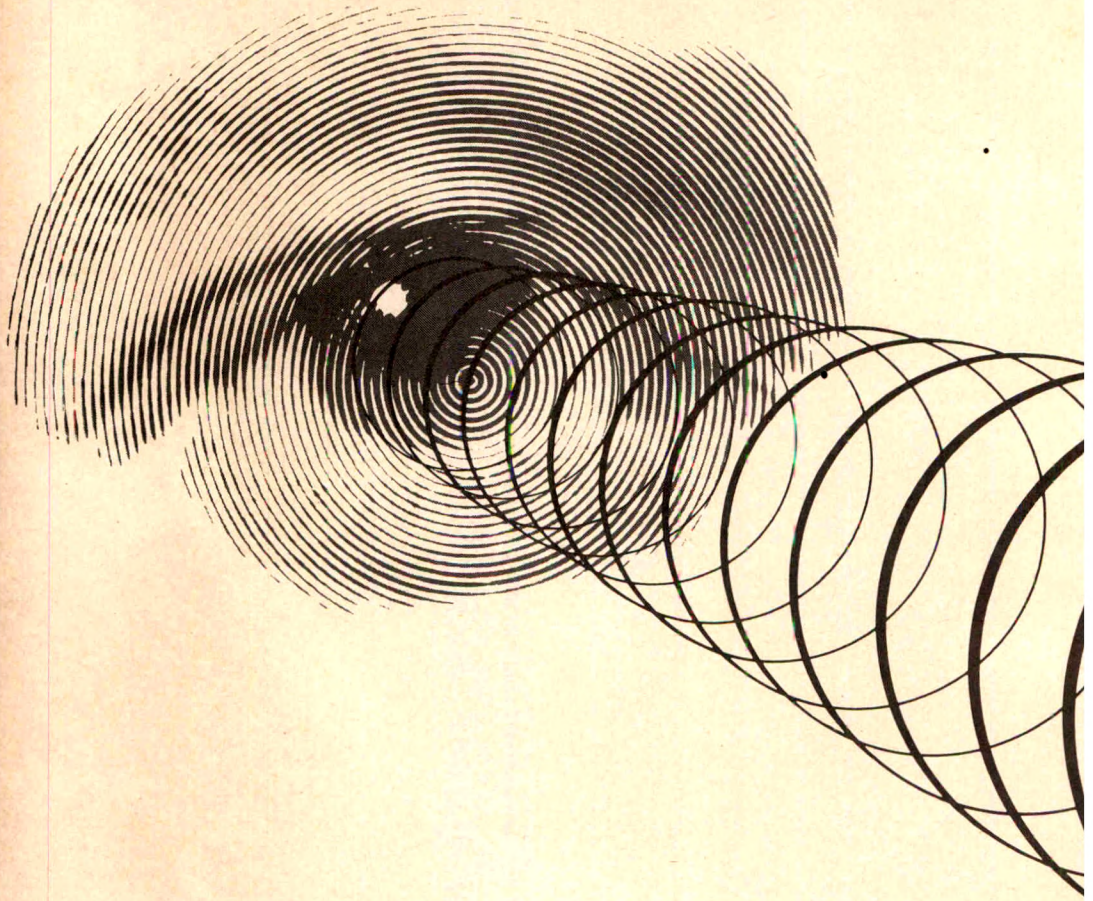
Resist bending and breaking.
Sharp, strong, ductile.
Honed 24 additional times
for superior penetration.

ETHICON

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For uninterrupted control of I.O.P.
...never more than one or two instillati



Scanning electron microsc
primate trabecular meshwork (X

Viewed here is Schlemm's
along with uveal and corneo
meshwork. (Photo cc
Douglas R. Anderson

This area is the site of the
pathologic changes whi
responsible for glaucoma a
focus of most of the m
procedures for treatment of the di

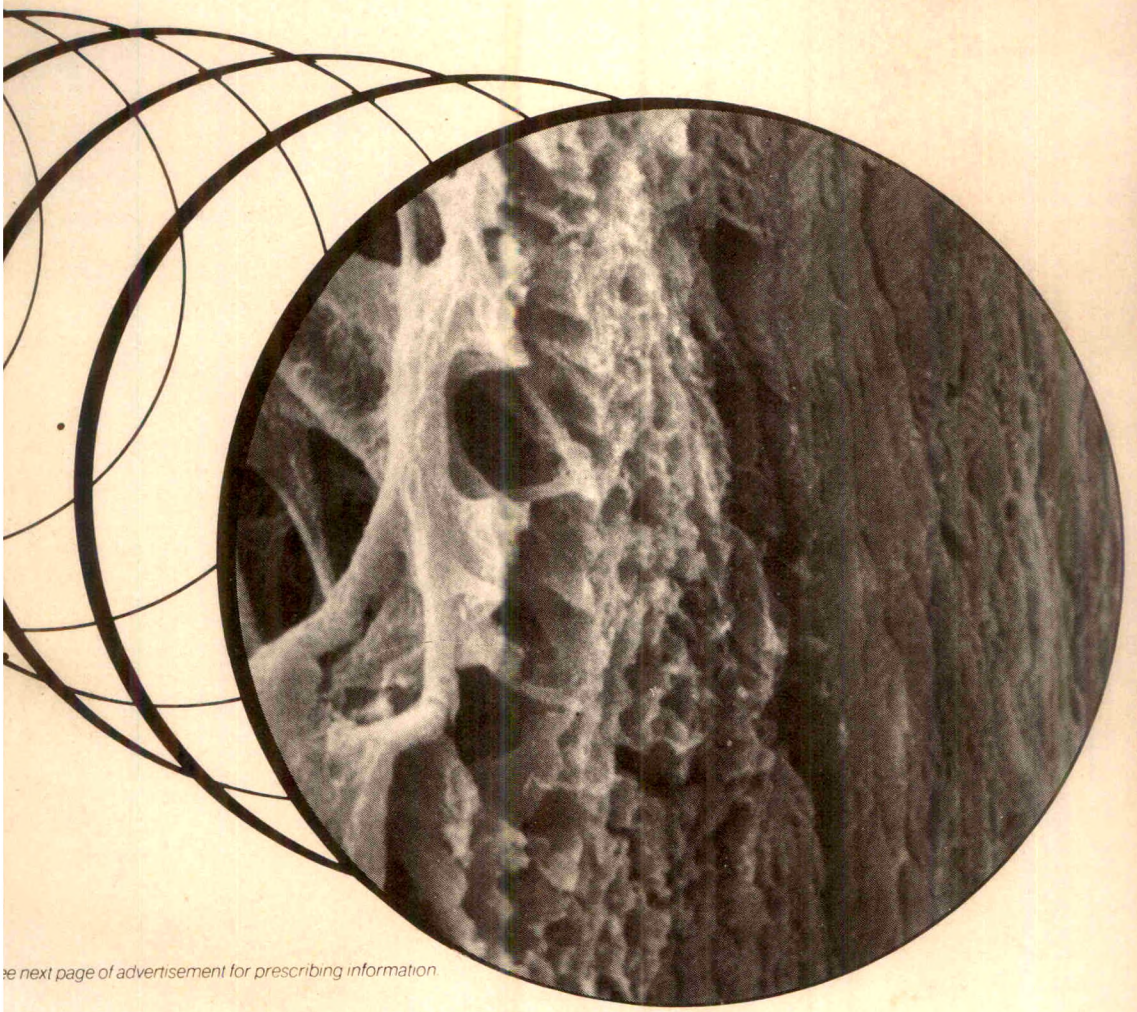
ecause PHOSPHOLINE IODIDE is long-acting, it can help provide
ninterrupted control of intraocular pressure in chronic simple (open-angle)
aucoma or glaucoma secondary to aphakia. Just one or, at most,
o instillations of PHOSPHOLINE IODIDE (one at bedtime, and, if necessary,
ne in the morning) are generally needed.

Although PHOSPHOLINE IODIDE is longer-acting than other miotics,
s *not* more potent. With four concentrations available, it offers a high degree of
osage flexibility for uninterrupted control of intraocular pressure...used alone
in combination with other medication.

When starting PHOSPHOLINE IODIDE therapy, 0.03%—the lowest strength—
the logical choice. If strengths of 0.06%, 0.125%, or 0.25% are required,
e initial use of the 0.03% will be helpful in smoothing the transition.

PHOSPHOLINE IODIDE® not more potent... but longer-acting

echothiophate iodide for ophthalmic solution)



ee next page of advertisement for prescribing information.

PHOSPHOLINE IODIDE®
(echothiophate iodide)
in the management of chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia

BRIEF SUMMARY
(*For full prescribing information, see package circular.*)
PHOSPHOLINE IODIDE® (echothiophate iodide)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia—Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.]

7315

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New York, N.Y. 10017



The new generation of disposable cryoextractors

Reliability is the keynote of the all new 2001. Eight proven design changes project the 2001 into a totally new product generation.

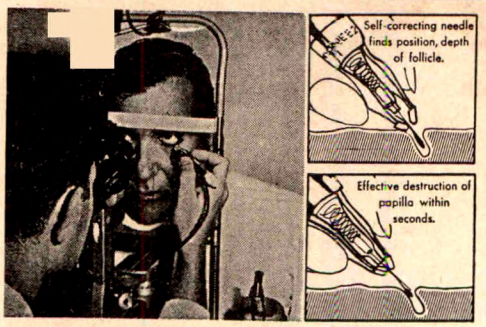
The 2001's unique 10 second delayed response feature allows you to go on warm for maximal adherence and ice ball formation. It is the only simple disposable with this singular advantage of warm or cold contact. With a running time in excess of two minutes you have ample margin time to compensate for any minor interruptions.

The 2001 has the advantage of being a fine surgical instrument rather than just a gas container with a spout or delivery tube. Compare these published list prices:

2001	$ 8.50
Cryophake	$12.50
F 20/20 Defrostable	$16.25
Microphake	$20.00

Our confidence is so high we will put our mouth where our money is. —Free Offer— Write for the new 2001 on your RX blank and attach a corner from this ad. We will send you 2 free sterile 2001's, without obligation.

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This permanent hair remover features the only patented self-correcting needle in existence. Battery operated instrument sterilizes itself when current flows. No-puncture safety feature also helps prevent infection. Simple enough to be used by laymen (for cosmetic purposes only).

Thousands of units sold for such varied professional application as removal of inverted eyelashes to cosmetic use.

Clinically tested (copy on request).

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**2nd ANNUAL
ROCKY MOUNTAIN
NEURO-OPHTHALMOLOGY
COURSE**

**SANTA FE HILTON INN
Santa Fe, New Mexico
February 5, 6, 7, 1976**

FACULTY

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This course will include lectures and seminar sessions covering basic disorders of ocular motility and the visual system. Ample time between sessions has been provided for leisure activity in Santa Fe and the nearby ski area.

Tuition: $175.00 provides transportation by chartered bus between hotel and ski facilities, one breakfast and evening banquet.

Residents Tuition: $75.00 upon application by their department head.

Registration limited: checks payable to:
Neuro-Ophthalmology Course
Department of Neurology
1007 Stanford Drive, N.E.
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GARAMYCIN®
brand of
gentamicin sulfate, U.S.P.
OPHTHALMIC
Solution-Sterile
Ointment-Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci; and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species, including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

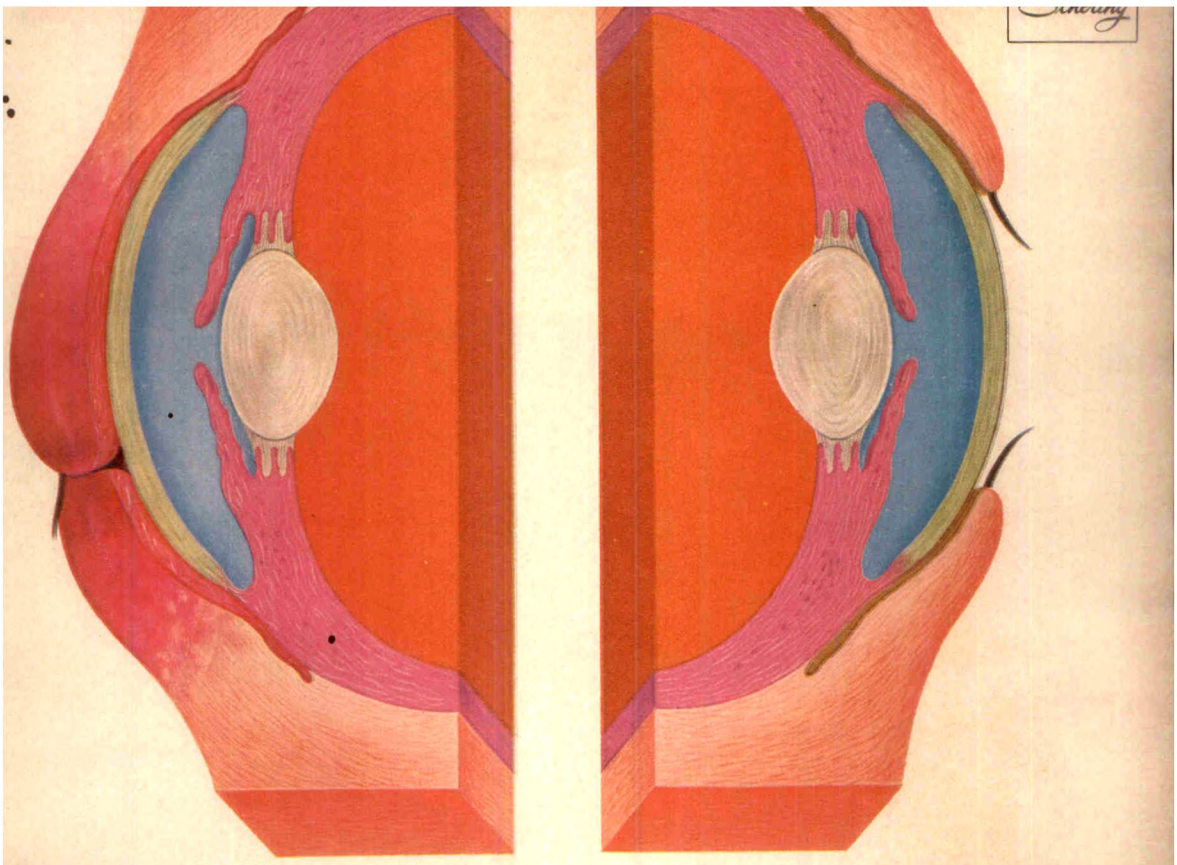
HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube, boxes of one and six. Store away from heat.

NOVEMBER 1973

For complete details, consult package insert or literature available from your Schering Representative; or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

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Kenilworth, N.J. 07033



The eye opener in bacterial conjunctivitis

Clears up conjunctivitis and other infections of the xternal eye and adnexa due to susceptible strains of ram-negative *H. influenzae, E. coli, K. pneumoniae, . lacunata, Enterobacter aerogenes* (formerly *Aero- acter*), *H. aegyptius* and *Neisseria* sp., including *. gonorrhoeae.*

Clears up conjunctivitis and other infections of the xternal eye and adnexa due to susceptible strains of ram-positive staphylococci and streptococci, cluding *D. pneumoniae*.

■ Clears up infections* of the external eye and adnexa due to problem organisms: *P. aeruginosa* (certain strains) and *Proteus* sp. (sensitive strains, both indole-positive and -negative).

■ Clears up infections* of the external eye and adnexa generally without sensitivity reactions and irritation. No significant organism resistance to date. This may occur in the future. Resistance to gentamicin has been produced (with difficulty) *in vitro* by repeated exposures.

Clears up external eye infections* caused by a wide range of ocular pathogens

*due to susceptible organisms.

WIDE GRAM-NEGATIVE SPECTRUM AND GRAM-POSITIVE ACTIVITY

GARAMYCIN® OPHTHALMIC

rand of gentamicin sulfate, U.S.P.

Solution-Sterile
Ointment-Sterile

ach ml. or gram contains gentamicin sulfate quivalent to 3.0 mg. gentamicin.

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Practitioners nationwide rely on the AO Contact Lens Division to design and fabricate lenses to meet their most difficult fitting problems. Among our most frequently requested special lenses are:

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- *Lenticular Bitoric*—For aphake patients with a high degree of corneal toricity.

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Call today...we are ready to help solve your non-standard problems with specially ground, high quality contact lenses.

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CONTACT LENS DIVISION
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Phone: 402-464-0246

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James H. Berglund, General Manager

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☐ The economy and efficiency of our *Master Control*™ method...the most comprehensive system available for lens fitting and inventory.

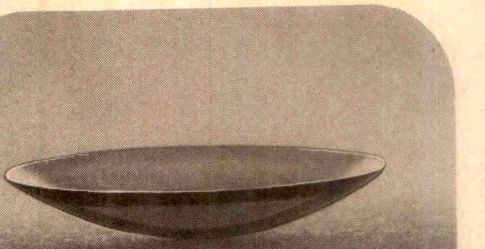
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How to Solve Contact Lens Acuity Problems

Reduced acuity caused by residual astigmatism of 1.25 D or less can be successfully corrected with the *Panofocal*™ lens.

Designed with an aspheric front surface, the *Panofocal* lens corrects spherical aberration rather than residual astigmatism. This reduces the circle of least confusion on the retina and, while not decreasing the residual astigmia, results in improved vision.

No special procedures are required to fit the *Panofocal* lens. Use your normal fitting criteria, making sure the lens centers well. Then, refract over the lens. The AO Contact Lens Division will use the sphere equivalent of your over-refraction to determine the power of the *Panofocal* lens and will then create the required aspheric front surface on a new lens.

Fitting convenience and cost, coupled with proven ability to produce improved visual acuity, make the *Panofocal* a worthwhile lens of choice when a moderate amount of residual astigmatism is present. We invite you to write for additional information.

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LENSES: WHITE, PINK AND GREEN

Why settle for high-index molded blanks when you can get immediate delivery on semi-finished single vision? Check the availabilities below in Schott's S-1005 White S-1205 Pink or the new Green, then call or write to Younger for prompt shipment!

58mm ROUND

Base Curves	Back Curves and Center Thickness				
	-8D 4mm	-10D 4mm	-10D 10mm	-12D 4mm	-16D 4mm
Plano	●	●	●	●	●
2.25	●	●	●	●	●
3.00	●	●	●	●	●
4.25	●	●	●	●	●
6.00	●	●	●	●	●

Base Curves	EDGE THICKNESS Back curve: -6.00 Plano available (*)					
	6mm	8mm	10mm	12mm	14mm	16m
Plano	●	●	●	●	●	●
2.25	●	●	●	●	●	●
3.00	●	●	●	●	●	●
4.25	●	●	●	●	●	●
6.00	●	●	●	●	●	●
8.00			Plano back only			
10.00						

63mm ROUND

Base Curves	Back Curves and Center Thickness			
	-8D 4mm	-10D 5mm	-12D 5mm	-16D 5mm
Plano	●	●	●	●
2.25	●	●	●	●
3.00	●	●	●	●
4.25	●	●	●	●
6.00	●	●	●	●

Base Curves	EDGE THICKNESS Back curve: -6.00 Plano available (*)					
	6mm	8mm	10mm	12mm		16mm
Plano	●	●	●	●		●
2.25	●	●	●	●		●
3.00	●	●	●	●		●
4.25	●	●	●	●		●
6.00	●	●	●	●		●
8.00	●					

71mm ROUND

Base Curves	Back Curves and Center Thickness		
	-6D 5mm	-8D 5mm	-10D 5mm
3.00	●	●	●
4.25	●	●	●
6.00		●	●

Base Curves	EDGE THICKNESS Back curve: -6.00D Plano available (*)					
		8mm	10mm	12mm		16mm
Plano		●	●	●		●
2.25		●	●	●		●
3.00		●	●	●		●
4.25		●	●	●		●
6.00		●	●	●		●

● = White, Pink, Green ● = White only * Plano back curve available only in White, Plano and 2.25 base

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Sterile Dacriose®
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Formula: A sterile, stable, buffered isotonic solution of boric acid, sodium carbonate, potassium chloride. Preserved with benzalkonium chloride, 0.01%; with 0.01% disodium edetate.
Warning: Do not dilute or reuse the solution. Do not touch dropper tip to eye or any surface as this may contaminate solution.
Note: Plastic irrigators must not be autoclaved and should not be heated above 170°F.
How Supplied: Sterile 0.50 fluid ounce (15 ml.), 0.90 fluid ounce (27 ml.), and 4 fluid ounce (125 ml.) plastic irrigator bottles. Not for injection.

SMP Division
Cooper Laboratories (P.R.), Inc.
San German, Puerto Rico 00753

Diamox® preserves the panorama

Acetazolamide

DIAMOX retards loss of peripheral vision in glaucoma* by reducing secretion of aqueous humor and thus intraocular pressure.



Diamox–all forms

Acetazolamide

*In chronic simple (open-angle) glaucoma and secondary glaucoma.

Before prescribing, consult package insert.

Indications: Tablets and Parenteral only: For adjunctive treatment of: edema due to congestive heart failure; drug-induced edema; centrencephalic epilepsies (petit mal, unlocalized seizures). **All forms:** Chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Contraindications: When sodium and/or potassium serum levels are depressed, in marked kidney and liver disease or dysfunction, suprarenal gland failure and hyperchloremic acidosis. Long-term use in chronic noncongestive angle closure glaucoma.

Warning: Although teratogenic and embryocidal effects demonstrated in mice at more than ten times the equivalent therapeutic doses have not been evidenced in humans, do not use DIAMOX in pregnancy, especially during the first trimester, unless expected benefits outweigh these potential adverse effects.

Precautions: Increasing the dose may increase drowsiness and paresthesia and decrease diuresis. Adverse reactions common to all sulfonamide derivatives may occur: fever, rash, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, agranulocytosis. Early detection is advised and if such occur, discontinue drug and institute appropriate therapy.

Adverse Reactions: Short-term therapy: (minimal) paresthesias, particularly a "tingling" feeling in the extremities; some loss of appetite, polyuria, drowsiness, confusion. Long-term therapy: An acidotic state may supervene usually corrected by bicarbonate. Transient myopia.

Other: (occasional) urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, convulsions.

Diamox® Sequels® add convenience to control

Acetazolamide Sustained Release Capsules 500 mg. b.i.d.



Diamox® Sequels® Offer:

Simple b.i.d. Schedule

Once-in-the-morning, once-in-the-evening regimen reduces likelihood of skipped doses.

Prolonged Therapeutic Effect

Sustained release of medication achieves continuous drug action to effectively decrease secretion of aqueous humor.

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Continuous drug action helps even out erratic peak-pressure periods.

And DIAMOX Acetazolamide does not interfere with the activity of miotics or other topicals. In fact, it often provides a complementary effect when used with miotics.

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125 mg./250 mg. Tablets

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Sodium Acetazolamide Vials of 500 mg.
with sodium hydroxide to adjust pH to approximately 9.2

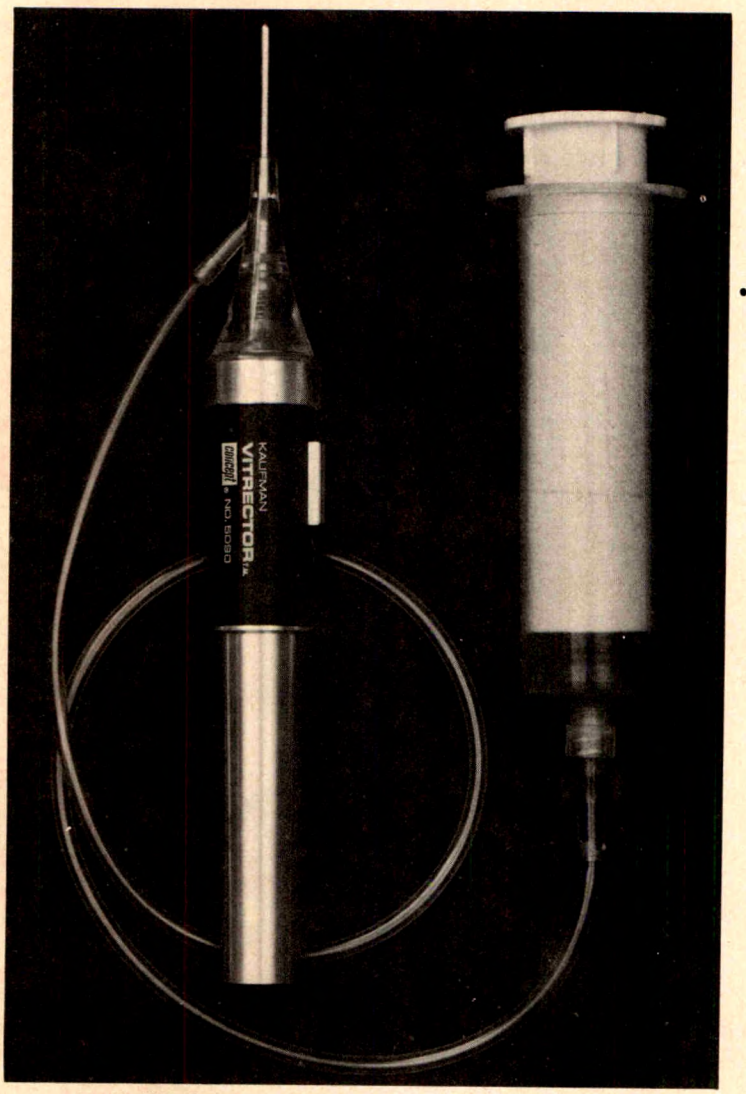
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A Division of American Cyanamid Company, Pearl River, New York 10965

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A 60-second way to remove vitreous? Yes.



You can spend up to 20 minutes or more removing vitreous during cataract surgery or keratoplasty. The KAUFMAN VITRECTOR™ does it in about a minute — easily, with little traction on the vitreous and without risk of severe granulomas and inflammation.

- The KAUFMAN VITRECTOR is new from Concept. It consists of a re-usable, battery-powered unit and a separate, sterile disposable kit, including cutting head, plastic syringe and suction tube. Also included with each kit is a latex sleeve which easily slips over the power unit, so it can be re-used without sterilization. Keep the KAUFMAN VITRECTOR close-at-hand. If vitreous loss occurs, just slip the power unit into the latex sleeve, snap-on the cutting head and connect the suction tube and syringe. It's ready-to-use. The assistant can observe the vitrectomy, and using the syringe, apply just the right amount of suction. It's fast, efficient, and convenient. It's also proven. Ask for the KAUFMAN VITRECTOR — from Concept.

Cat. No. 5090 Power Unit for VITRECTOR

Cat. No. 5091 Sterile Disposable KAUFMAN VITRECTOR Kit (including cutting head, suction syringe and connecting tubing)

We put ideas to work.

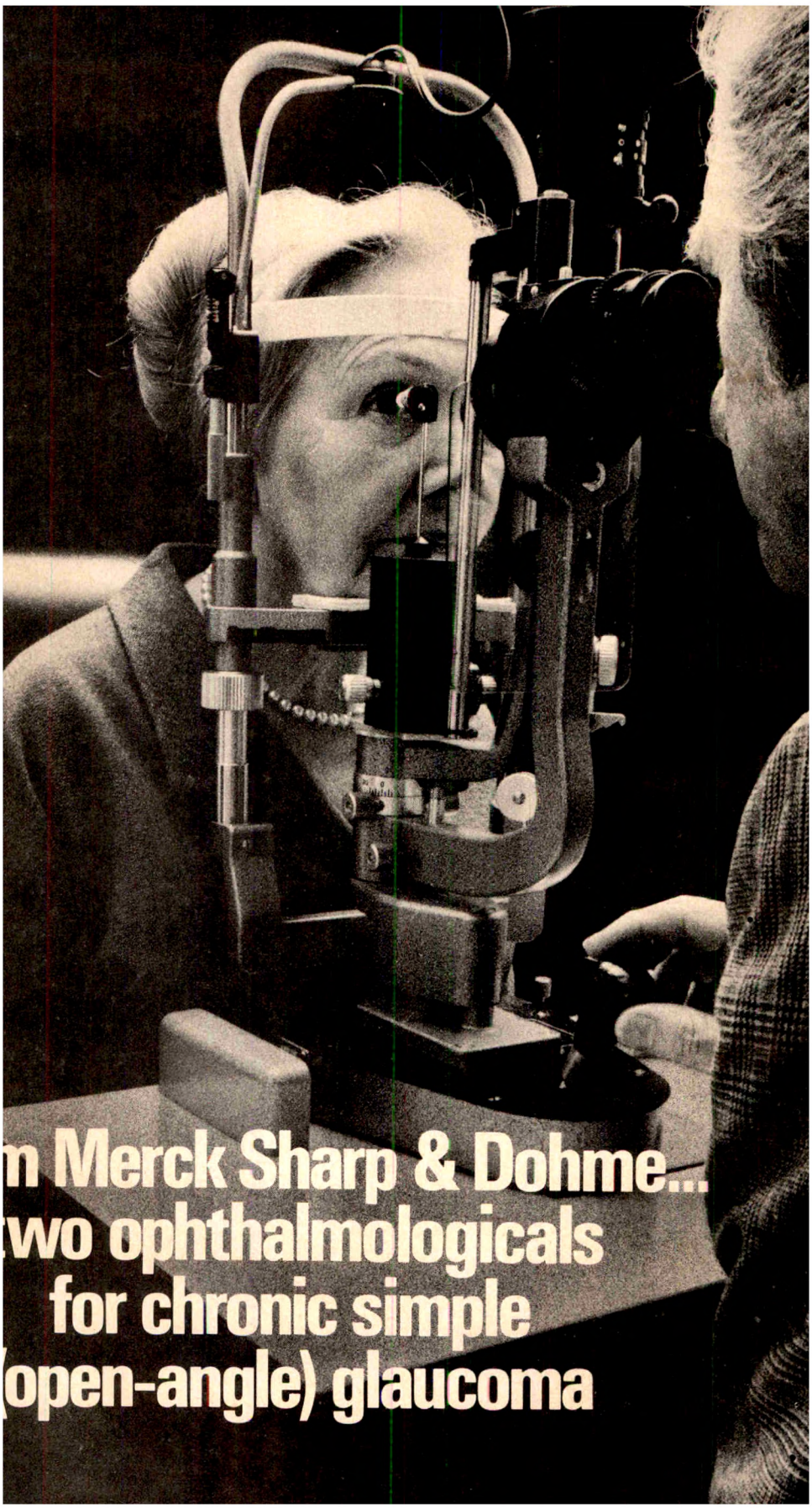
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Clearwater, Florida 33516

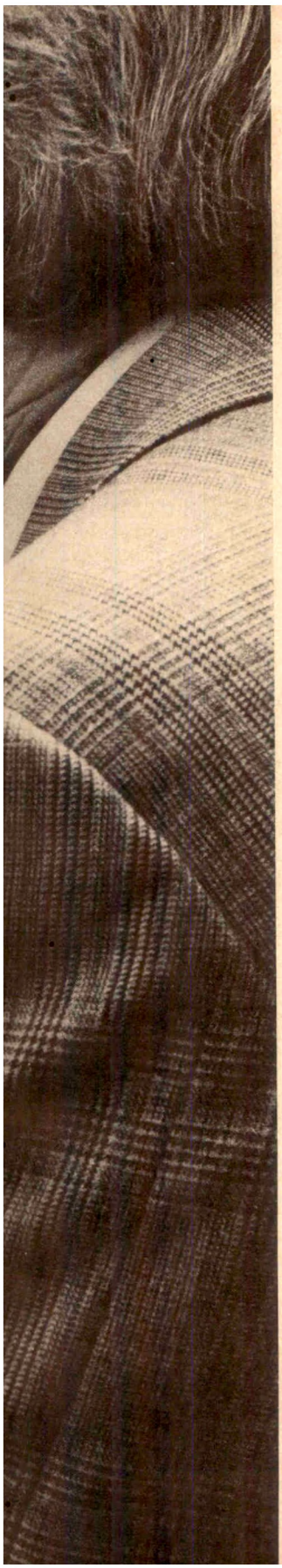
concept INC.

We provide "automatic pati recall" for more than 7,000 eye care specialists

When requested by the eye care specialist, our computers can autom notify holders of over 400,000 RLI policies of their annual check up For information on this program, write Replacement Lens, Inc., 902 North Lindbergh Drive, Peoria, Illinois 61614




m Merck Sharp & Dohme...
two ophthalmologicals
for chronic simple
(open-angle) glaucoma



When a highly potent long-acting miotic is needed...

OPHTHALMIC SOLUTION, 0.125% and 0.25%

HUMORSOL®

(DEMECARIUM BROMIDE | MSD)

- Needs no refrigeration
- Needs no reconstitution
- Needs no eyedropper
- Stable at room temperature for three years

HUMORSOL is contraindicated in patients with known hypersensitivity to the drug, in active uveal inflammation, and in most cases of narrow-angle glaucoma.

When baseline miotics aren't enough...

TABLETS, 50 mg

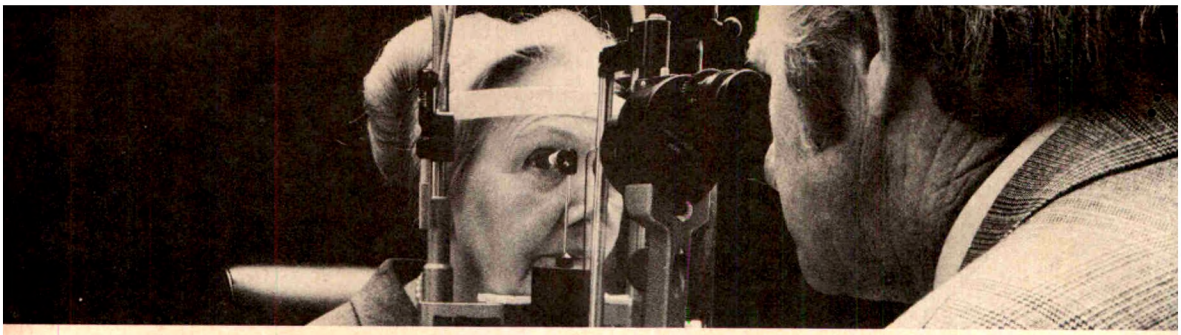
DARANIDE®

(DICHLORPHENAMIDE | MSD)

- Oral carbonic anhydrase inhibitor
- Partially suppresses secretion of aqueous humor
- Best used as adjunct to miotics
- Onset of action usually within an hour; maximal effect is observed in 2 to 4 hours
- Lowered intraocular pressure may be maintained for 6 to 12 hours

DARANIDE is contraindicated in hepatic insufficiency, renal failure, adrenocortical insufficiency, hyperchloremic acidosis, or in conditions in which serum levels of sodium or potassium are depressed. It should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased.

For brief summaries of prescribing information on DARANIDE and HUMORSOL, please see following page.



OPHTHALMIC SOLUTION, 0.125% and 0.25%

HUMORSOL®

(DEMECARIUM BROMIDE | MSD)

FOR TOPICAL APPLICATION INTO THE CONJUNCTIVAL SAC ONLY

Contraindications: Known hypersensitivity; active uveal inflammation; most cases of narrow-angle glaucoma.

Warnings: Should be administered with extreme caution to patients with myasthenia gravis who are on systemic anticholinesterase therapy; conversely, systemic anticholinesterase drugs for myasthenia gravis should be added cautiously. Succinylcholine should be administered with extreme caution before or during general anesthesia, because of possible respiratory and cardiovascular collapse.

Use in Pregnancy: Safe use in pregnancy has not been established, nor has the absence of adverse effects on the fetus or on respiration of the neonate. During pregnancy weigh potential benefits against possible hazards.

Precautions: Gonioscopy is recommended before therapy. Do not use, or use cautiously, when an intraocular inflammatory process is present.

Compression of the lacrimal sac during and following instillation for a minute or two minimizes drainage into the nasal chamber. Wash hands immediately after instillation. Discontinue use if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, or cardiac irregularities occur.

Persons exposed to organophosphate-type insecticides and pesticides (gardeners, organophosphate-manufacturing plant or warehouse workers, farmers, residents of communities which are undergoing insecticide spraying or dusting, etc.) should be warned of added systemic effects possible from absorption through the respiratory tract or skin. Wearing of respiratory masks, frequent washing, and clothing changes may be advisable.

Use with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects. Use extreme caution before intraocular surgery because of the possibility of hyphema.

Despite observance of all precautions, repeated administration may cause depression of the concentration of cholinesterase in the serum and erythrocytes, with resultant systemic effects.

Adverse Reactions: Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, brow ache, headache, and induced myopia with visual blurring; activation of latent iritis or uveitis; retinal detachment has been reported occasionally. Iris cysts may form, enlarge, and obscure vision, more frequently in children; cysts usually shrink when the miotic is discontinued but, rarely, may rupture or break free into the aqueous. Frequent examination is advisable.

Prolonged use may cause conjunctival thickening and obstruction of nasolacrimal canals. If systemic effects occur (e.g., salivation, urinary incontinence, nausea, abdominal cramps, vomiting, diarrhea, dyspnea, bradycardia, cardiac irregularities), parenteral administration of atropine is indicated: 0.4 to 0.6 mg or more for adults, proportionately less for children; artificial respiration may be required. Similar therapy is indicated for overdosage.

Lens opacities have been reported, and routine slit-lamp examinations should accompany prolonged use. Paradoxical increase in intraocular pressure may occur and be alleviated by a mydriatic.

Dosage and Administration: Initial titration and dosage adjustments must be individualized to obtain maximal therapeutic effect. Patient must be observed closely during initial period. If response is not adequate within first 24 hours, consider other measures. Keep frequency of use to a minimum in all patients, but especially in children.

Since technic is crucial to proper and safe administration, consult prescribing information for full details.

Supplied: In 5-ml OCUMETER® Ophthalmic Dispenser containing 0.125 or 0.25 percent solution and sodium chloride; benzalkonium chloride 1:5000 added as preservative.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

TABLETS, 50 mg

DARANIDE®

(DICHLORPHENAMIDE | MSD)

Contraindications: Hepatic insufficiency, renal failure, adrenocortical insufficiency, hyperchloremic acidosis, or conditions in which serum levels of sodium or potassium are depressed. Should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased.

Warning: *Use in pregnancy:* Should not be used in women of childbearing age or in pregnancy, especially during the first trimester, unless the benefits to be expected outweigh potential adverse effects.

Precautions: Potassium excretion is increased and hypokalemia may develop with brisk diuresis, when severe cirrhosis is present, or during concomitant use of steroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Hypokalemia may be avoided or treated by use of potassium chloride or giving foods with a high potassium content. Use with caution in severe respiratory acidosis.

Adverse Reactions: Side effects (characteristic of carbonic anhydrase inhibitors) may include gastrointestinal disturbances (anorexia, nausea, vomiting), loss of weight, constipation, urinary frequency, renal colic, renal calculi, mild skin eruptions, pruritus, leukopenia, agranulocytosis, thrombocytopenia, headache, weakness, nervousness, globus hystericus, sedation, lassitude, depression, confusion, disorientation, dizziness, ataxia, tremor, tinnitus, and paresthesias of hands, feet, and tongue.

How Supplied: Tablets containing 50 mg dichlorphenamide each, in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

MSD
MERCK SHARP & DOHME

NOW IN NEW 25-D LENS, LARGE & SMALL SIZES

VOLK

Conoid Lenses® for Indirect Ophthalmoscopy



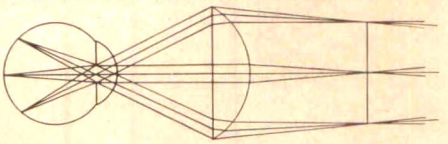
NOW FEATURED IN CLEAR WHITE
OR SOLID YELLOW OPHTHALMIC
CROWN GLASS

World-famous Volk diagnostic lenses are immediately available! Each lens has a front ASPHERIC surface, precision ground and polished, and an exact coacting spherical back surface, producing superior illumination of the fundus, greater patient comfort and tolerance, and an aberration-free aerial image of the fundus. Our yellow lenses reduce total radiant energy for greater safety and comfort by removing unnecessary blue and violet light. Larger diameter lenses for examination and large field of view; smaller lenses for retinal surgery and observation. Order from leading ophthalmic instrument dealers. Send for technical bulletin.

SPECIFICATIONS

POWER	LARGE DIAMETERS	STANDARD DIAMETERS
14-D	52 mm.	45 mm.
20-D	48 mm.	35 mm.
25-D	45 mm.	33 mm.
30-D	43 mm.	31 mm.

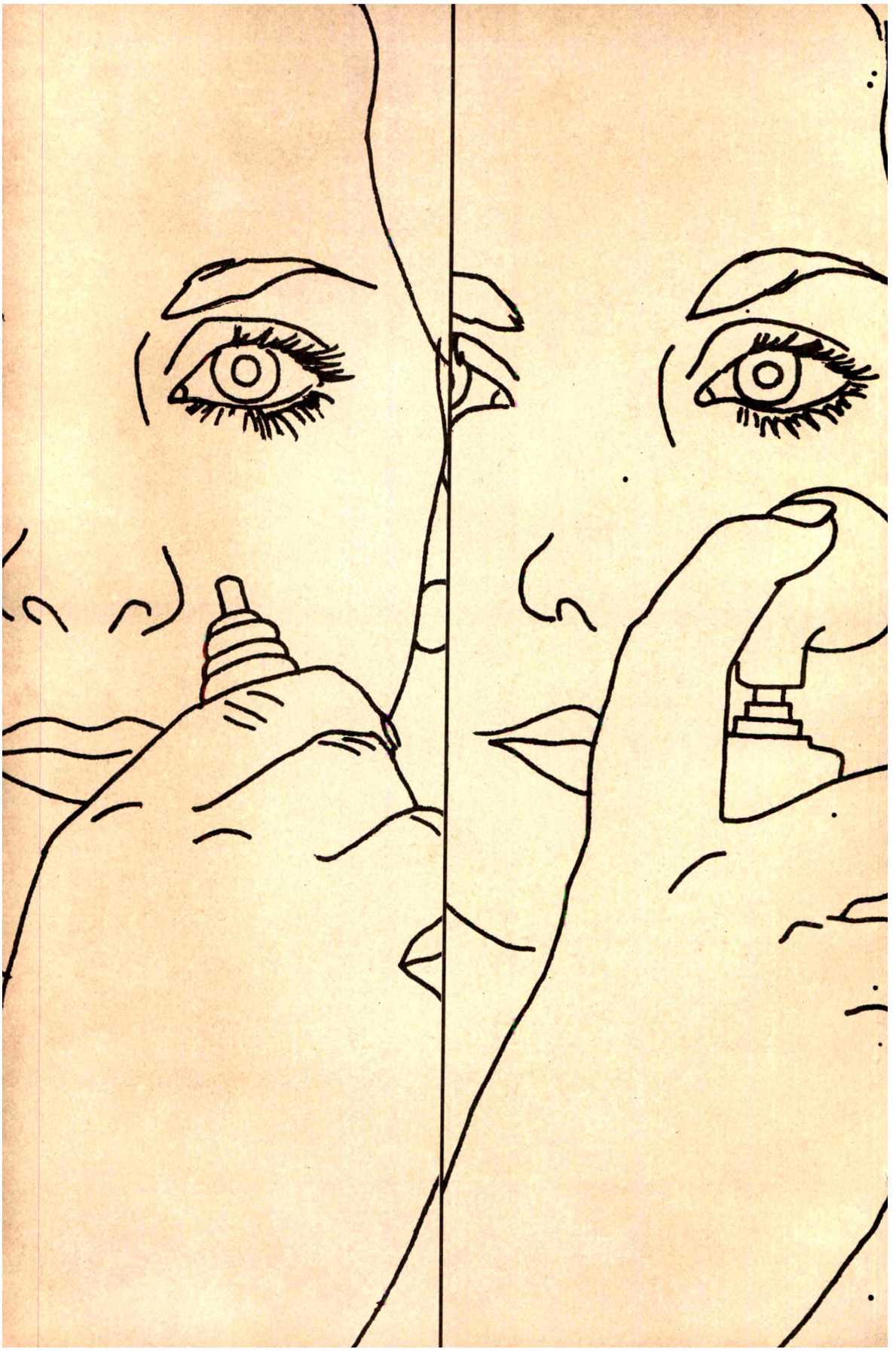
DIAGRAM SHOWING LARGE, CLEAR, UNDISTORTED 3-DIMENSIONAL AERIAL IMAGE PRODUCED BY VOLK CONOID LENS



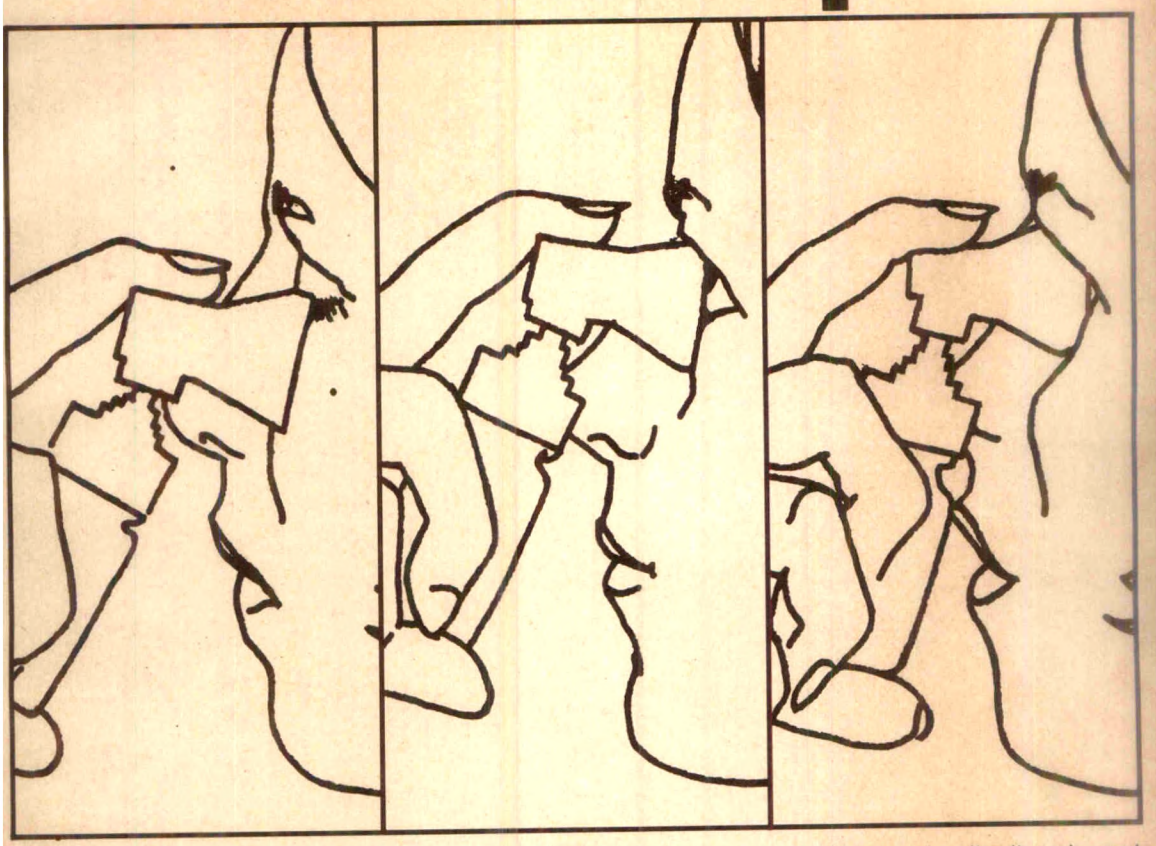
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VOLK CONOID® REGISTERED TRADEMARK



A better way to take a drop?



Hold MISTURA between finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.

Used properly, MISTURA can assure complete coverage of the absorbing surface of the eye. Its supraorbital fit avoids eye contact. MISTURA offers easy self-application, economy of full dose, on target delivery, and a minimum of wasted medication.

MISTURA®

Ophthalmic Spray Products



Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965 213-5

Please see prescribing information on last page of this advertisement.

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.
NOTE: Not for use with the soft contact lens.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev.7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for the difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES
1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 as a preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P *pilocarpine HCl* is indicated for:
1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

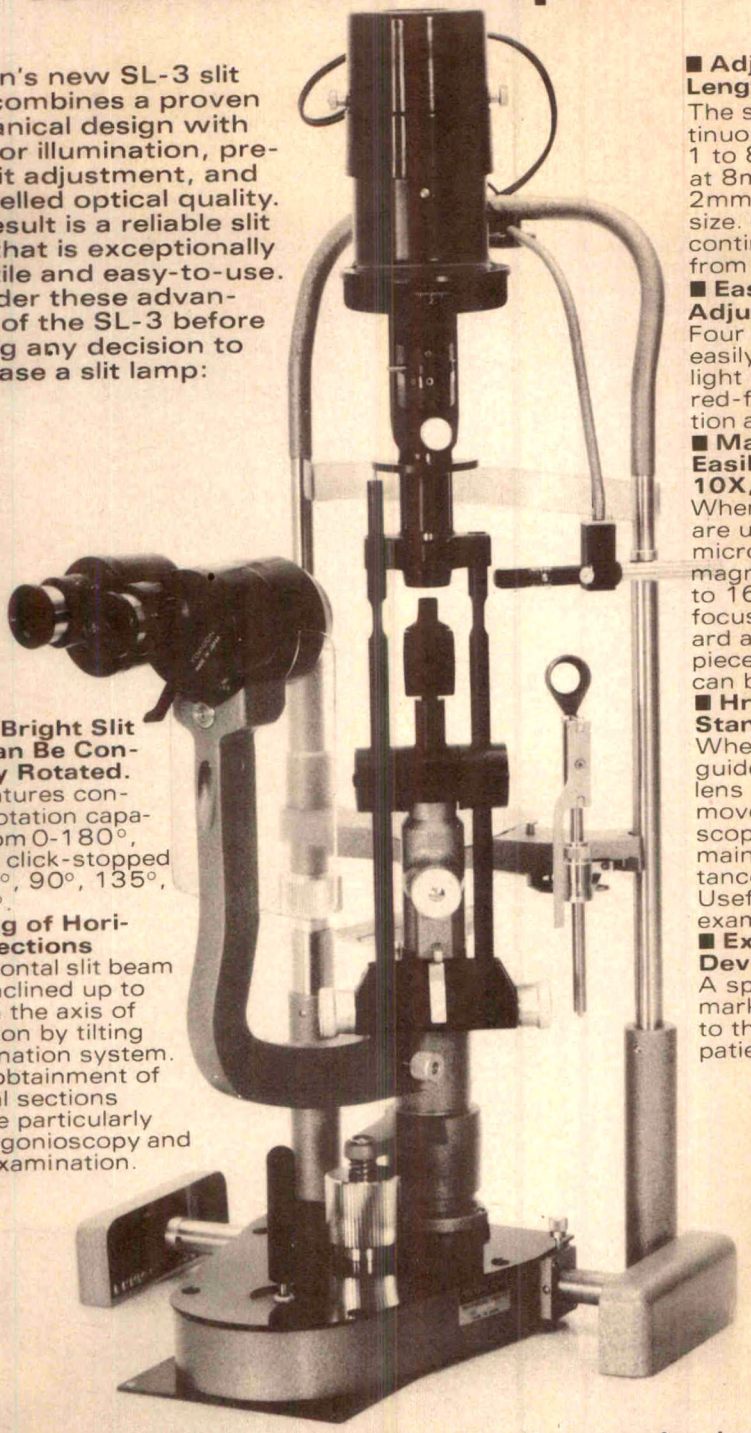
PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on prolonged use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:
1. For glaucoma, the recommended dosage is 1 mist application two to four times a day of the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations should be used.
3. The dosage and strength required to reverse mydriasis depends on the cycloplegic used.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965 212-5

Is Joined With Topcon Quality

Topcon's new SL-3 slit lamp combines a proven mechanical design with superior illumination, precise slit adjustment, and unexcelled optical quality. The result is a reliable slit lamp that is exceptionally versatile and easy-to-use. Consider these advantages of the SL-3 before making any decision to purchase a slit lamp:



■ **Sharp, Bright Slit Image Can Be Continuously Rotated.** Image features continuous rotation capabilities from 0-180°, or can be click-stopped at 0°, 45°, 90°, 135°, and 180°.

■ **Viewing of Horizontal Sections** The horizontal slit beam may be inclined up to 20° from the axis of observation by tilting the illumination system. Permits obtainment of horizontal sections which are particularly useful in gonioscopy and fundus examination.

■ **Adjustable Slit Length And Slit Width** The slit length is continuously variable from 1 to 8mm, or click-stops at 8mm, 5mm, 3mm, 2mm, 1mm, or pinhole size. Slit width is also continuously variable from 0 to 8mm.

■ **Easy Filter Adjustments** Four filters can be easily inserted into the light path: cobalt blue, red-free, heat absorption and neutral density.

■ **Magnification Easily Adjustable to 10X, 16X, Or 25X.** When 10X eyepieces are used, lever on microscope allows magnification increase to 16X, without refocusing. With standard accessory 16X eyepieces, magnification can be increased to 25X.

■ **Hruby Lens Is Standard Accessory.** When attached to the guide plate, the Hruby lens is coupled to all movements of microscope while lens itself maintains same distance from the cornea. Useful for fundus examination.

■ **Exclusive Fixation Device.** A special fixation marker can be focused to the individual patient's refraction.

TOPCON SL-3

The Topcon SL-3 also offers several optional accessories, including the famous Goldman Applanation Tonometer for easy attachment. Best of all, the SL-3 IS AVAILABLE FOR PROMPT DELIVERY. Contact your local Topcon distributor or write to us for details.

TOPCON

A New World of Precision Optics

Topcon Instrument Corp. of America, 170 Fifth Avenue, New York, N.Y. 10010 (Dept. SL3-AJO)

Here's what you can expect.

The lathe-cut, soft, hydrophilic contact lens, now available from Soft Lenses, Inc.

First, you can expect a high quality finished product. Each lens is lathe-cut from a button of highly stable three-dimensional polymer.

It is hydrated under stringent controls and subjected to thorough quality assurance checks. All lenses are shipped to you in sterile vials.

You can expect good results from the unique advantages of our small trial fitting set. In fact, you can get started with our standard nine-lens set.

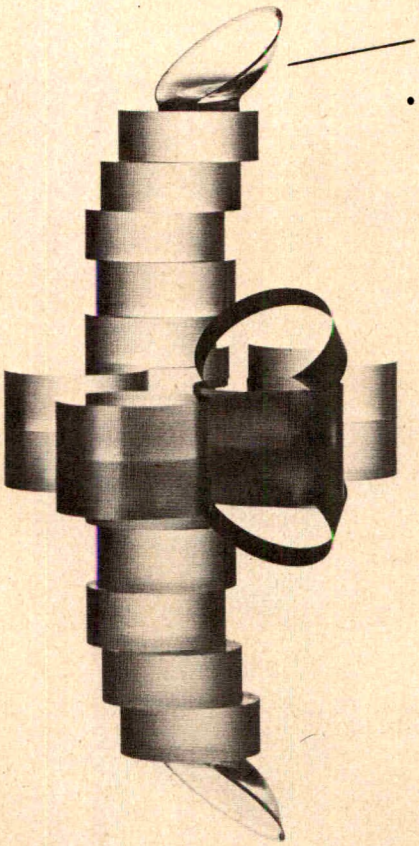
Yet this selection offers you a wide range of base curves and diameters. Enough to satisfy the majority of fitting problems in the correction of ametropia.

And only a few ancillary products are required.

With expanded production and our computer system, you can expect prompt attention to shipments, even the biggest ones. Of course, you always have direct communication with Soft Lenses Inc., through our toll-free numbers.

Our staff does virtually all the paper work. Technical representatives are also available in some areas.

To get complete information about Hydro-Curve™ products and supplies, call now, toll free (800) 854-2790 – in California (800) 542-6000. We're expecting your call.



The lathe-cut, soft, hydrophilic contact lens, now available from Soft Lenses, Inc.

The versatile one

HYDROCURVE™

(hefilcon A)

Contact Lens PHP*

From Soft Lenses, Inc.
A division of Continuous Curve Contact Lenses, Inc.
8006 Engineer Rd., San Diego, CA 92111

HydroCurve™ Soft Lenses, Inc. *PHP (U.S. Pat. 3,721,657) Trade Mark of Automated Optics, Inc.

DROCURVE™ (hefilcon A) CONTACT LENS

ated from PHP* polymer (poly (2-hydroxyethyl methacrylate) Water 54%)

CRIPTION—The HydroCurve® (hefilcon A) Contact Lens PHP* is mispherical shell of approximately 14 mm. chord diameter and 0.1 0 mm. thickness. It consists of 46% poly (2-hydroxyethyl acrylate) and 54% water by weight when immersed in normal e.

IONS—In its hydrated state a HydroCurve® (hefilcon A) Contact PHP* becomes soft and pliable. When placed on the human ea the hydrated lens acts as a refracting medium to compensate erical ametropias. The material has a refractive index of 1.43.

ICATIONS—HydroCurve® (hefilcon A) Contact Lenses PHP* are ated for the correction of visual acuity in persons with nondiseased who have spherical ametropias; refractive astigmatism of 1.50 ters or less and/or corneal astigmatism of 2.00 diopters or less.

NTRAINDICATIONS—HydroCurve® (hefilcon A) Contact Lenses * are contraindicated by the presence of any of the following ditions:

Acute and subacute inflammations of the anterior segment of the eye.

Any eye disease which affects the cornea or conjunctiva.

Insufficiency of lacrimal secretion.

Corneal hypoesthesia.

Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

RNINGS

dicants and Eye Drops: The HydroCurve® (hefilcon A) Contact s PHP* must be stored ONLY in BOILnSOAK® Solution. No thalmic solutions or medicants, including conventional contact lens utions, can be used by HydroCurve® (hefilcon A) Contact Lens P* wearers prior to or while the lens is in place on the eye. Also, no utions, including conventional contact lens solutions, other than ILnSOAK® and the recommended cleaners BOILnSOAK® or igel® or Soft/Mate® may be used on the HydroCurve® (hefilcon A) ntact Lens PHP* when the lens is off the eye.

rasions and Infections: If the lenses become less comfortable to the arer than when they were first placed on the wearer's corneas, this y indicate the presence of a foreign body. The lens should be moved immediately and the patient examined. If any eye abrasion, eration, irritation or infection is present, a physician should be nsulted immediately.

ns Sanitation: Patients must adhere to recommended daily sanitary e of the HydroCurve® (hefilcon A) Contact Lenses PHP*. Failure to ow this procedure may result in development of serious ocular ections.

aring Restrictions: The HydroCurve® (hefilcon A) Contact Lens P* should be removed before sleeping or swimming or in the sence of noxious and irritating vapors.

ual Blurring: When visual blurring occurs the lens must be removed til the condition subsides.

ECAUTIONS

orage: HydroCurve® (hefilcon A) Contact Lenses PHP* must be ired ONLY in BOILnSOAK® Solution. If left exposed to air, the lenses l dehydrate. If a lens dehydrates, it should be soaked in BOILnSOAK® lution until it returns to a soft, supple state.

eaning and Disinfecting: HydroCurve® (hefilcon A) Contact Lenses P* must be BOTH cleaned and disinfected daily. One procedure es not replace the other. CLEANING is necessary to move mucus and film from the lens surface. This can be complished by using either BOILnSOAK® or Pliagel® or ft/Mate® on a daily basis. Excessive deposits may damage e lens; therefore, if this occurs, review care of lens with tient.

DISINFECTING with the Hydrotherm® tient Unit and BOILnSOAK® Solution s been shown to prevent the growth certain organisms, namely aphylococcus aureus, Pseudomonas ruginosa, Bacillus subtilis, Candida bicans, and Herpes simplex, on the ns and in the HydroCurve® Carrying ase with the porta-FLOW® ansfer Unit (basket).

HydroCurve® (hefilcon A) ontact Lenses PHP* must be eaned daily with fresh BOILnSOAK® r Pliagel® or Soft/Mate.® Fresh OILnSOAK® Solution must be used aily for storing the lenses. The HydroCurve® Carrying Case must be emptied and refilled with fresh BOILnSOAK® Solution just before disinfecting the lenses.

If a Hydrotherm® Patient Unit is not available for disinfecting the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.

Hygiene: Patients must be instructed to wash and rinse hands thoroughly, and dry with a lint-free towel before handling the lenses.

Cosmetics, lotions, soaps and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS—Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, patients may be instructed to apply a few drops of BOILnSOAK® Solution and wait until the lens moves freely before removing it.

Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms.

Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION—Conventional methods of fitting contact lenses do not apply to HydroCurve® (hefilcon A) Contact Lenses PHP*. For a detailed description of the fitting technique, refer to the HydroCurve® Fitting Guide, additional copies of which are available from: Soft Lenses, Inc., 8006 Engineer Road, San Diego, California 92111.

There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

Day	Maximum Wearing Time (Continuous Hours)	Day	Maximum Wearing Time (Continuous Hours)
1	3	8	8
2	3	9	8
3	4	10	10
4	4	11	12
5	6	12	14
6	6	13	15
7	8	14	all waking hours*

*Lenses should never be worn 24 hours a day.

Care must be taken on the initial visit to assure that the patient is supplied with a HydroCurve® Patient Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.



In Use Durability: With normal use and patient care, HydroCurve® (hefilcon A) Contact Lenses PHP* have been shown to be durable for a minimum of one year.

HOW SUPPLIED—Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the base curve, dioptric power, diameter, thickness and the manufacturing lot number of the lens.

To assure proper lens care and handling, each HydroCurve® patient must be supplied with a complete HydroCurve® Patient Care Kit.

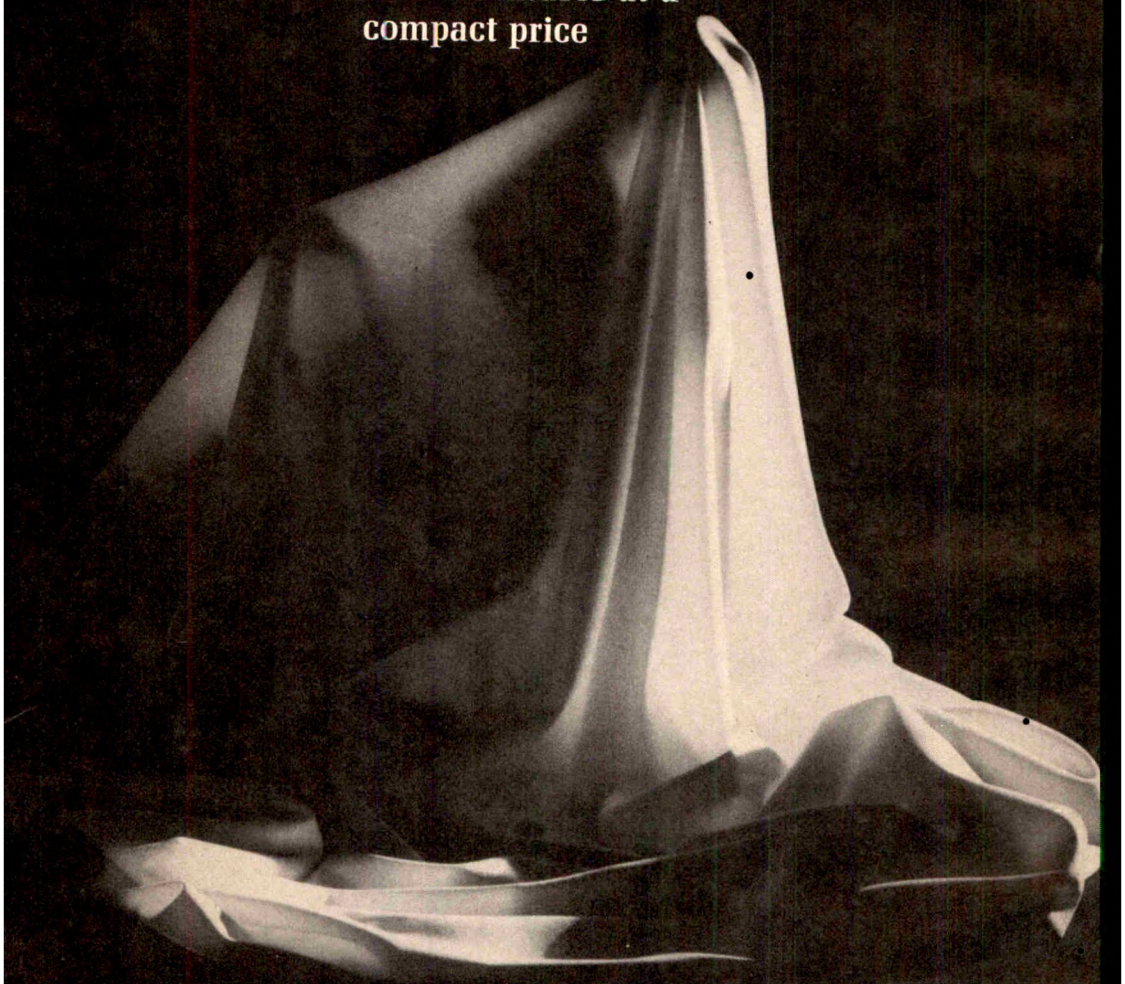
The HydroCurve® Patient Care Kit is a package required for lens cleaning, disinfecting and storing consisting of the following:

porta-FLOW® Transfer Unit (basket)	Cat. # 1001
HydroCurve® Carrying Case	Cat. # 1002
Hydrotherm® Patient Unit	Cat. # 1003
BOILnSOAK® Solution	Cat. # 1004
Pliagel® Sterile Cleaner (optional) or	Cat. # 1005
Soft/Mate® Sterile Cleaner (optional)	Cat. # 1006
Patient Instructions	Cat. # 1007

HydroCurve® Soft Lenses, Inc. *PHP (U.S. Pat. 3,721,657). Trademark of Autgmated Optics, Inc. Soft Lenses, Inc. is a division of Continuous Curve Contact Lenses, Inc. 8006 Engineer Road, San Diego, California 92111. © 1974 Continuous Curve Contact Lenses, Inc.

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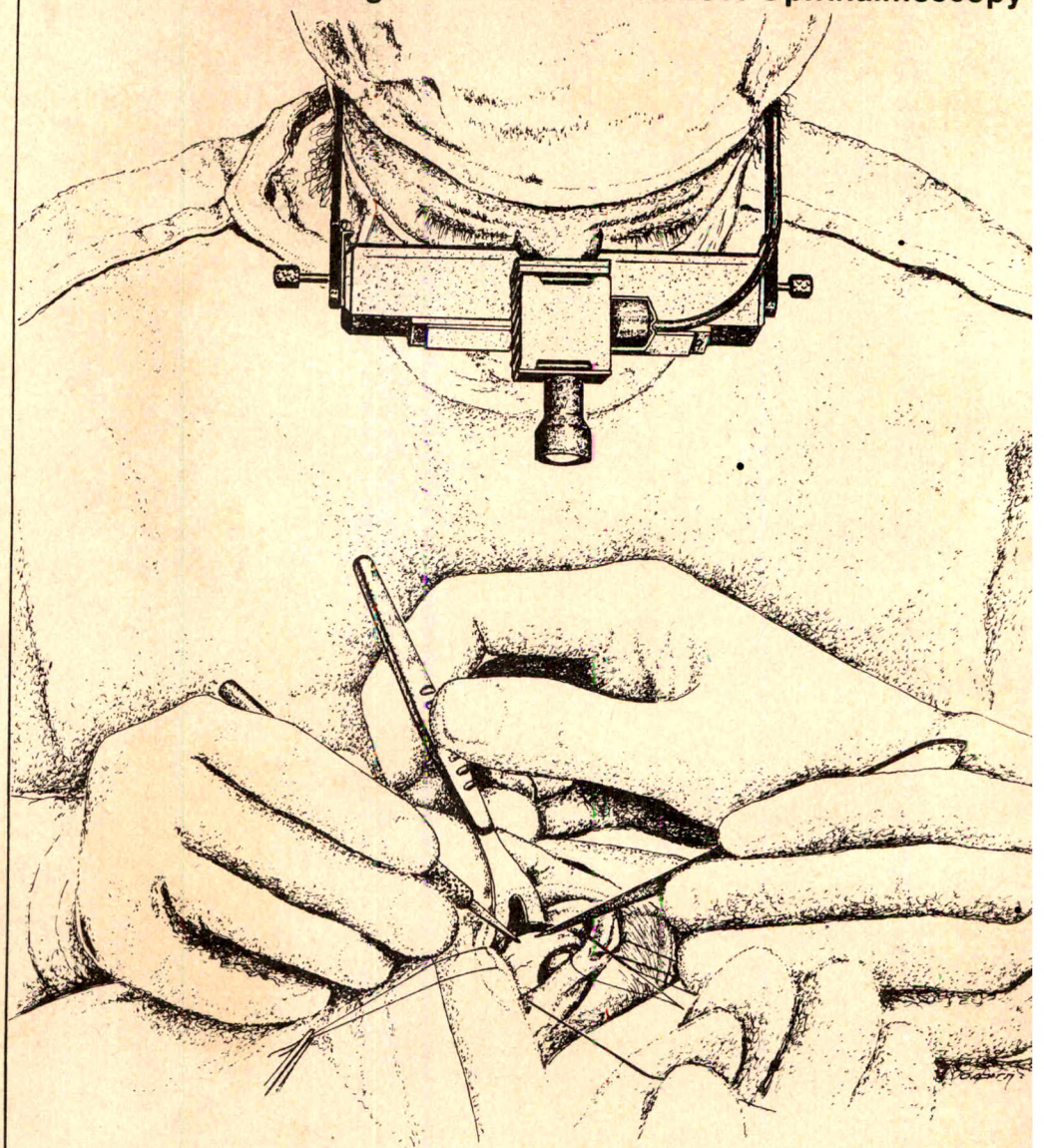
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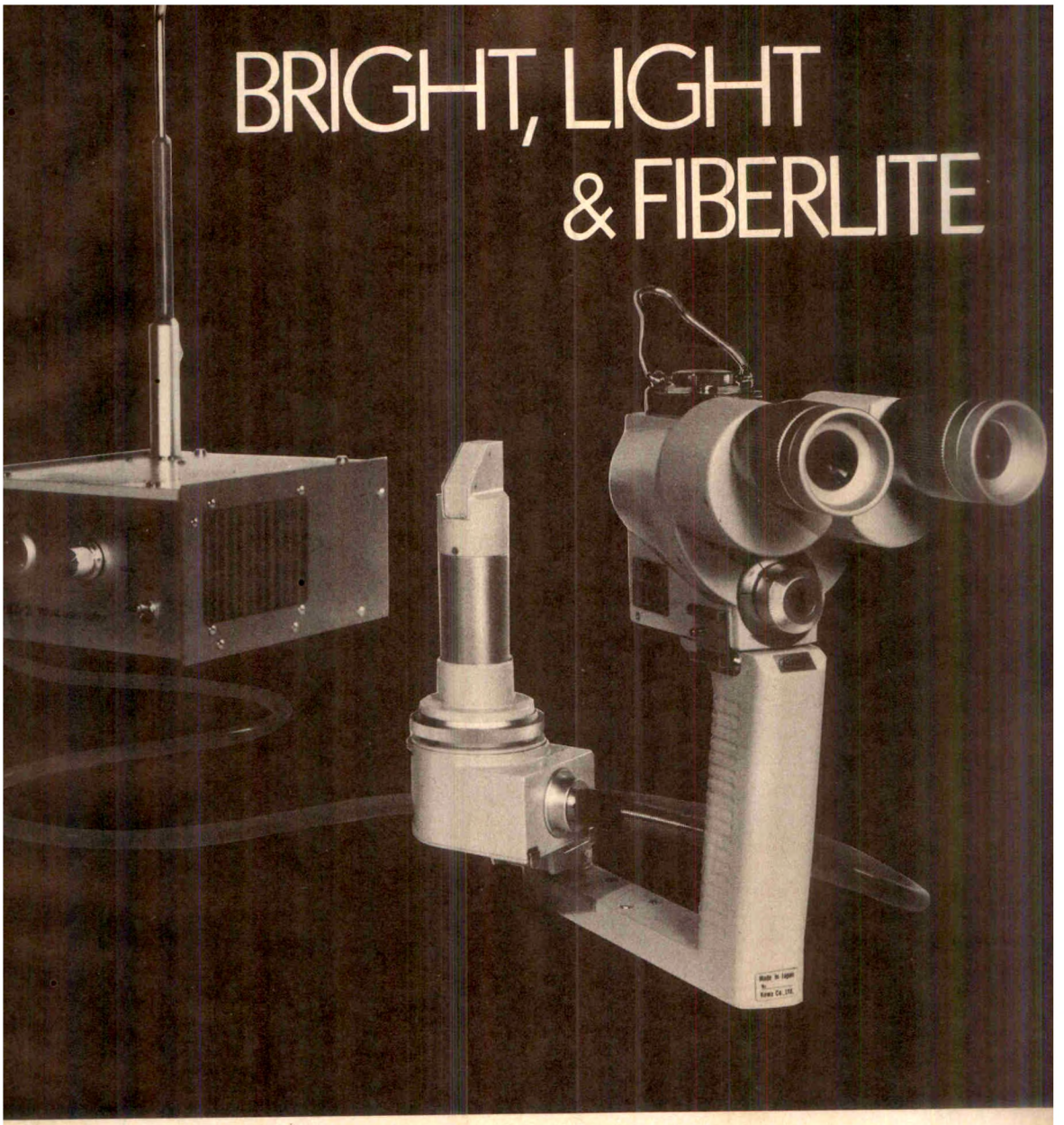
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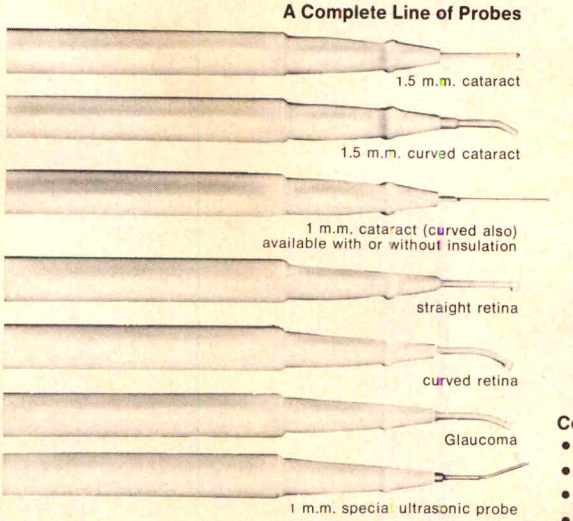
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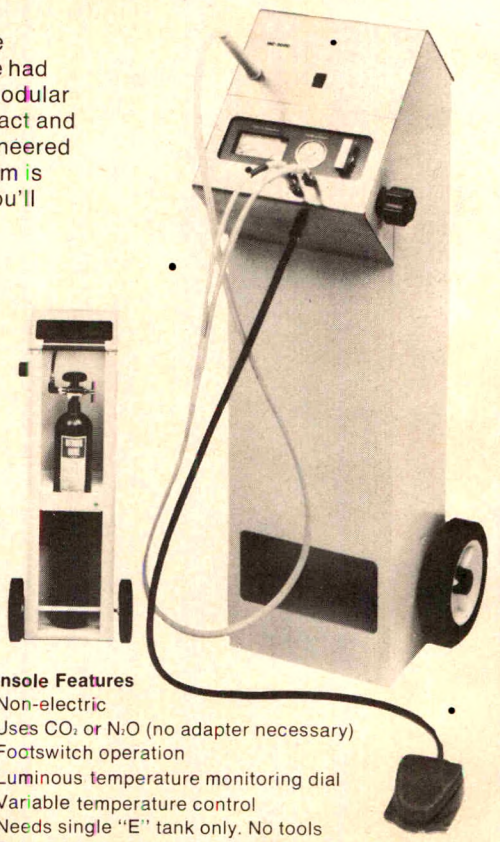


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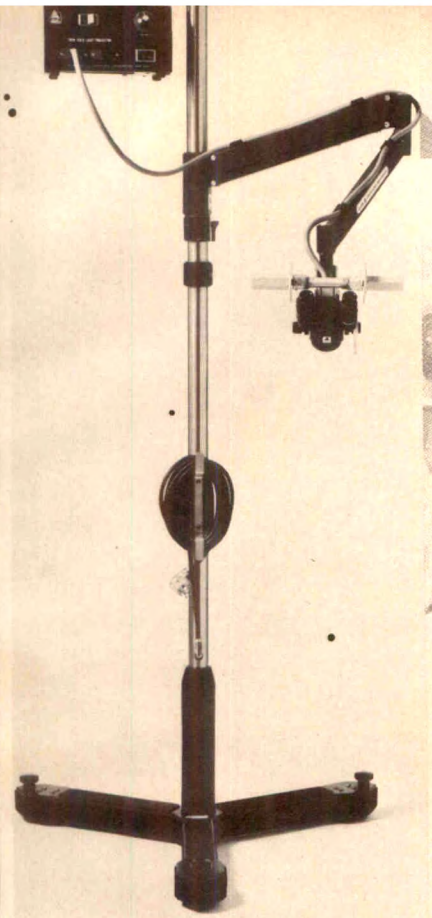
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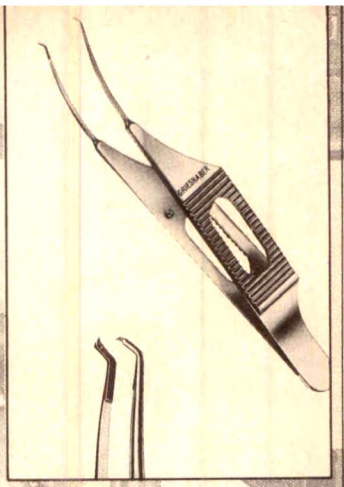
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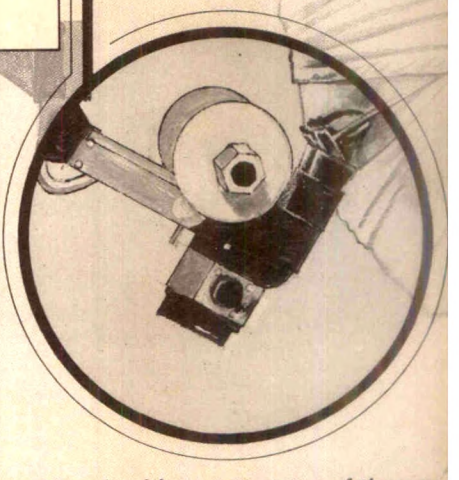
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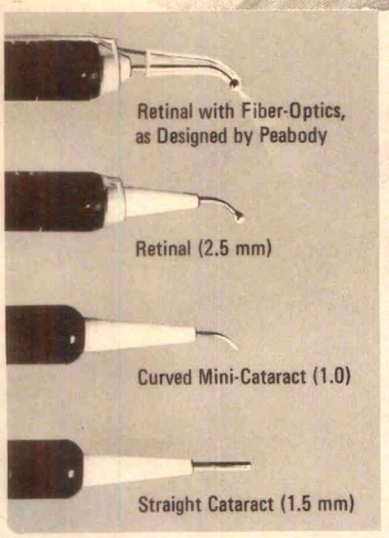
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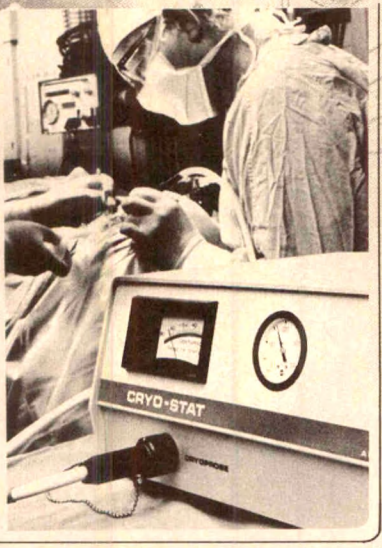


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Flexinyl's special aphakic design is used by over 400 practitioners. This ultra-small, thin, lightweight design solves a greater percentage of low-rider problems, off-center problems, and provides splendid V.A.

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This special Flexinyl® design actually helps to *rehabilitate the cornea.* Patients who have worn contact lenses for 5 to 10 years show signs of corneal steepening, flattening, induced astigmatism. Flexinyl® helps return the cornea to original K's within a relatively short time. Flexinyl's smaller O.Z.'s wider P.C.'s, ellipsoid P.C. curves, and thinness are key factors.

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The Flexinyl® Lens is backed by a 100% Money-Back Guarantee.

Telephone consultation

We'll be pleased to consult with you over the phone about Flexinyl® ability to solve fitting problems. From the Midwest and East, phone us at **800/621-4653.** (In Illinois, call collect 312/427-3575.) In the West, phone us at **800/421-0540.** (In California, call 800/252-0123.)

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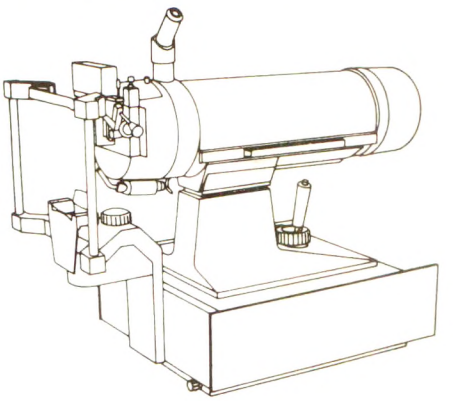
This seminar covers the basic principles and indications of the intraocular lens. The lens models presently used (Binkhorst, Copeland, Worst, Fiederov) will be described and the means used in implantation at the time of intracapsular, extracapsular and phacoemulsification cataract extraction will be demonstrated. The methodology of implanting an intraocular lens in an aphakic eye will be covered. Pre-operative, operative and post operative care will be emphasized. The long term results of the faculty members will be detailed. Formal lectures are combined with individual instruction.

Enrollment is limited and advance registration is required.

Fee: $100.00 (Residents $50.00)

Address Inquiries to Program Chairman: M. L. Kwitko, M.D., 5591 Cote Des Neiges Rd., Suite 1, Montreal, Canada. H3T-1Y8.

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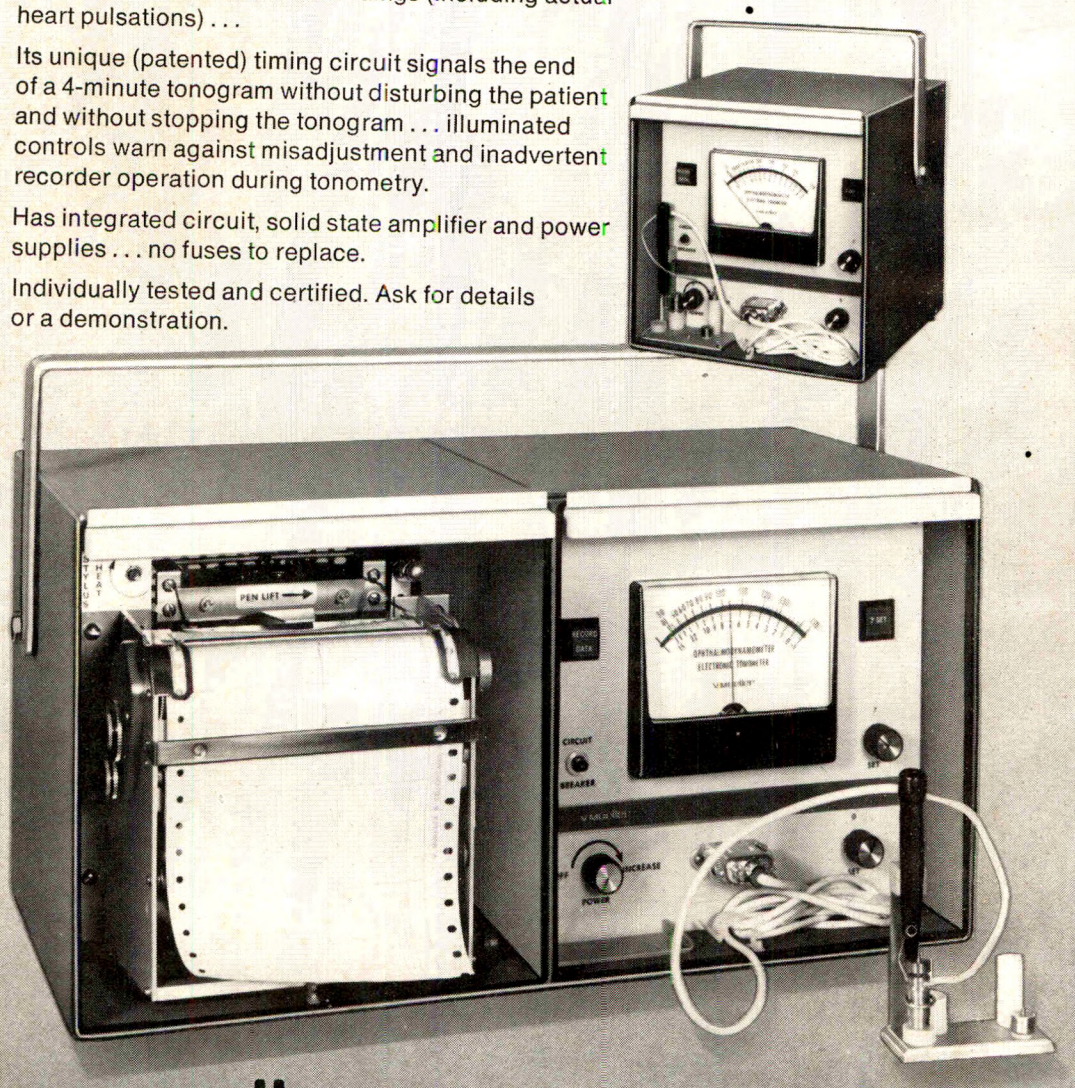
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About half the size and weight of earlier models .... easier to handle . . . easier to use . . . the newest V. Mueller Tonography Unit retains the accuracy and stability of those famous earlier models . . . and clear, inkless, rectilinear recordings (including actual heart pulsations) . . .

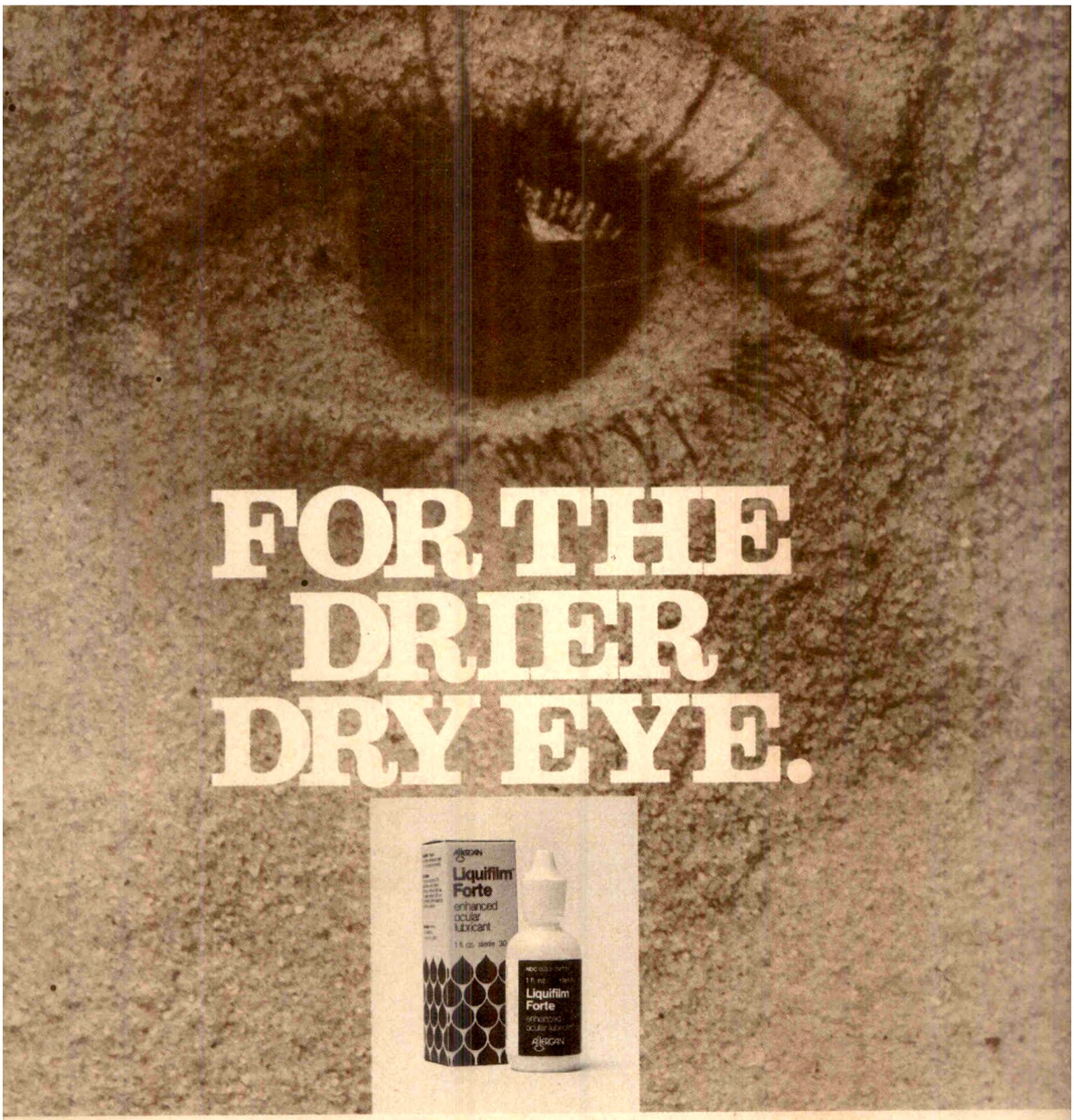
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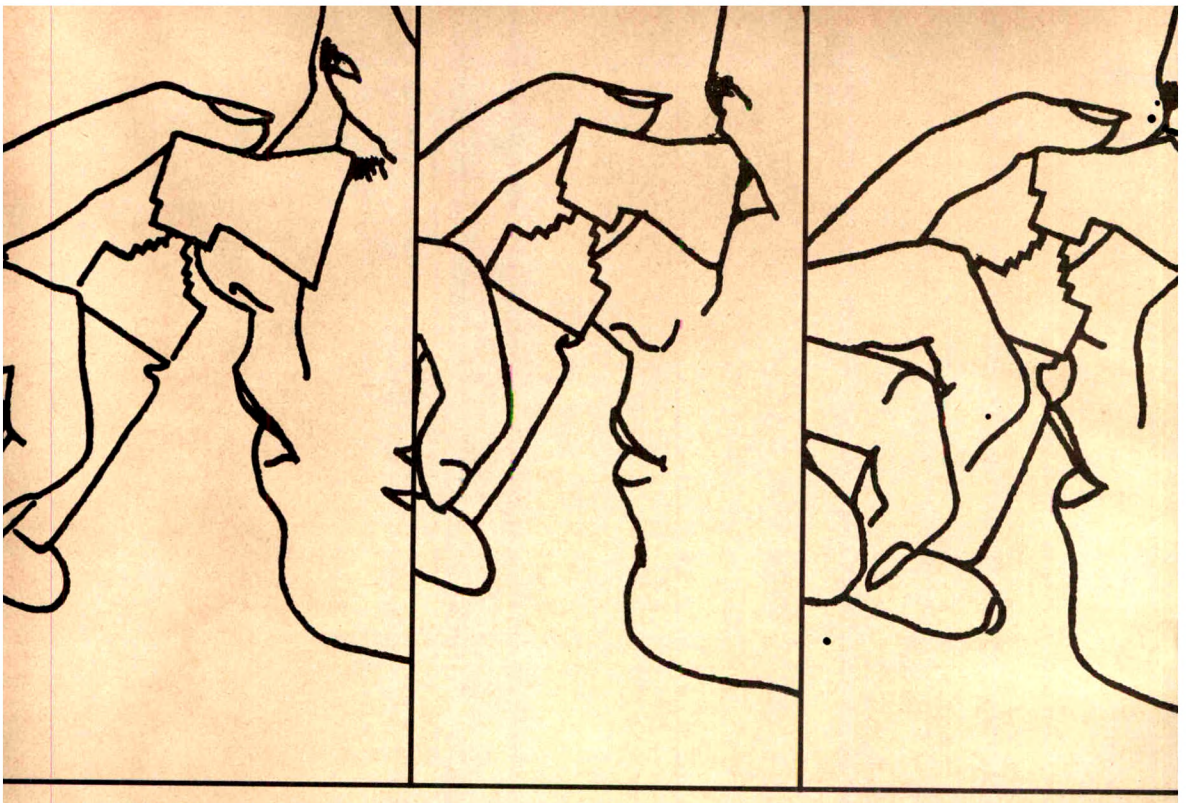
New Liquifilm Forte contains more than twice the usual polyvinyl alcohol concentration which combines with dextrose to produce optimum viscosity.

And optimum viscosity means prolonged relief from dry-eye itching and burning. Yet unlike more viscous tear substitutes, you'll hear a minimum of complaints of blurring or stickiness.

Designed for the chronic user, new Liquifilm Forte is balanced, buffered and isotonic for consistent comfort in the eye. And, new Liquifilm Forte is supplied in a full one ounce bottle for maximum patient economy.

Now you have a complete range of adjunctive dry-eye therapy from Allergan: Liquifilm® Tears for routine artificial tear use; Lacri-Lube® sterile ophthalmic ointment for nighttime lubrication; and new Liquifilm Forte...for the drier dry eye.

ALLERGAN IRVINE, CALIFORNIA 92664 / U.S.A.



Hold MISTURA between finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

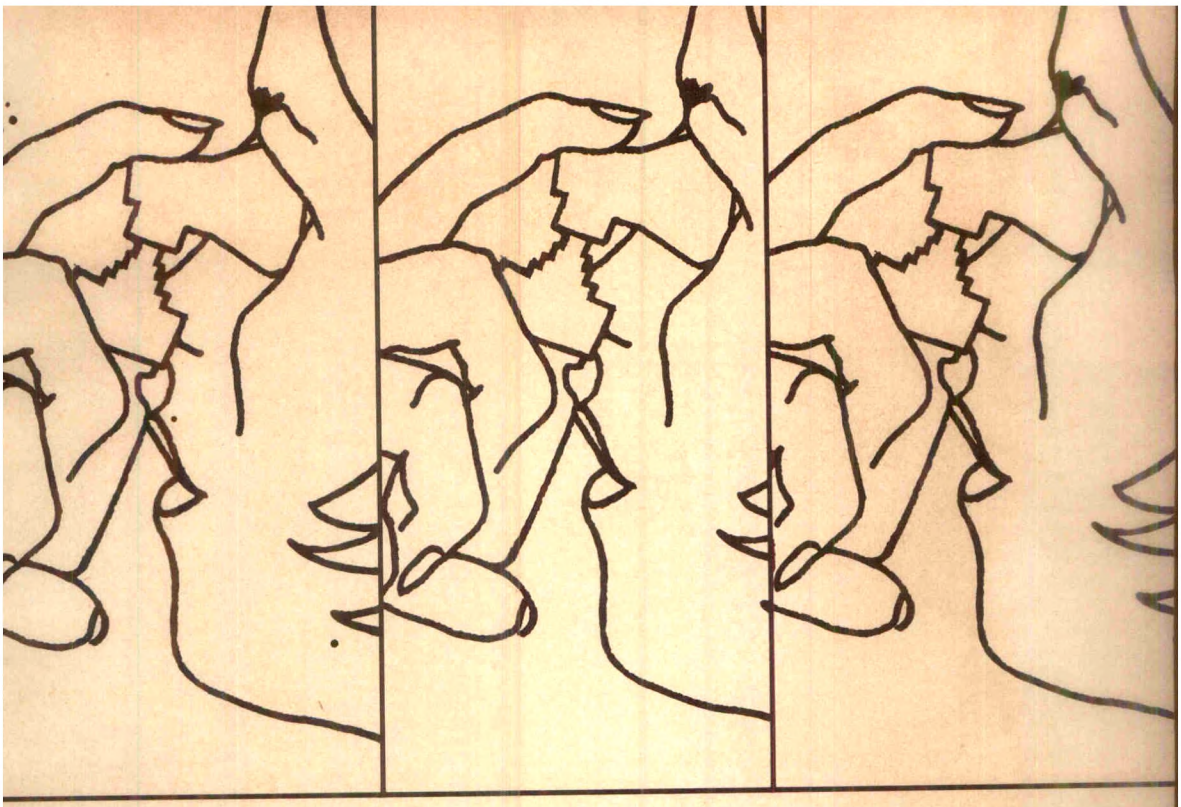
Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.



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Ophthalmic Spray Products



The longer they use it the better they like it.

168 dropper users tried MISTURA. 71% like it.† 28 ophthalmologists recently switched from dropper medication with pilocarpine to MISTURA® P Pilocarpine HCl. Acceptance increased with use. At the end of the first week, 63% liked it—by the second week, patient acceptance increased to 71%. Typical comments included:

"It's more convenient." "I don't have to tip my head." "Less trouble keeping my eyes open." "I can do it myself, my wife had to help me before." Is MISTURA a better way to deliver a drop? Most patients who try it think so!

†Data on file at Lederle Laboratories.

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Please see prescribing information on last page of this advertisement

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev.7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with: benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for the difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES
1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

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3. Use following treatment with cycloplegics to reverse mydriasis.

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HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

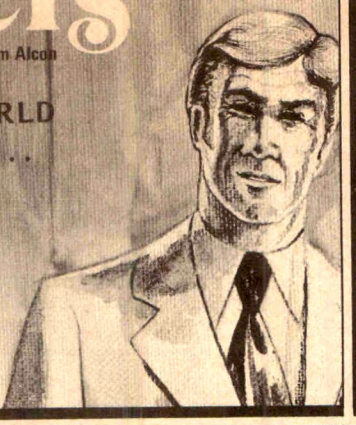
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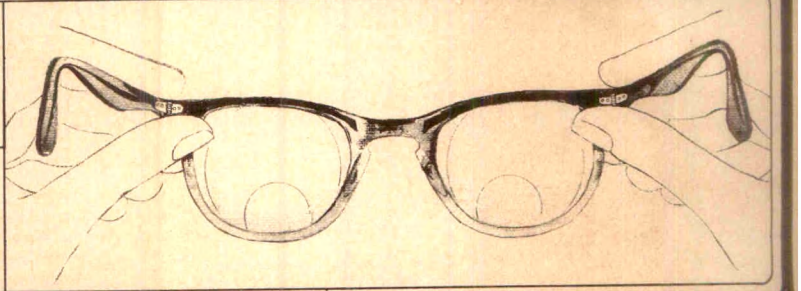


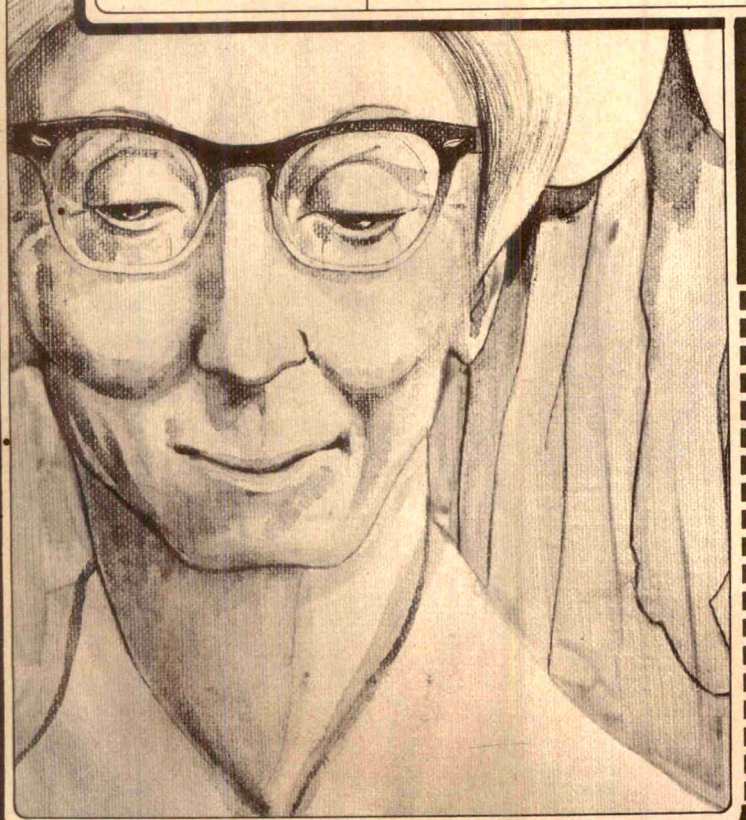
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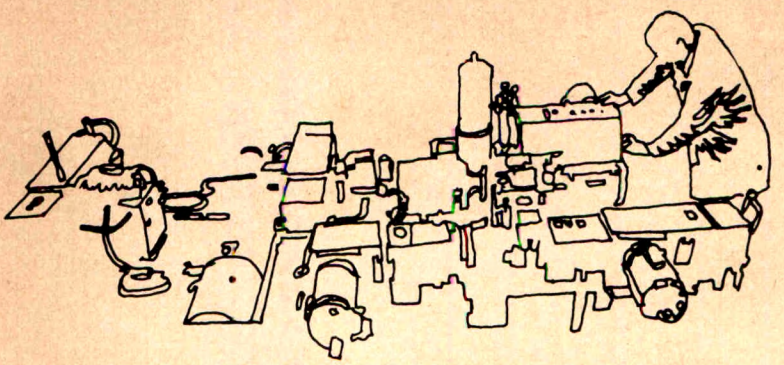
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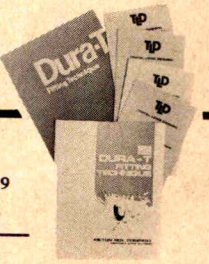
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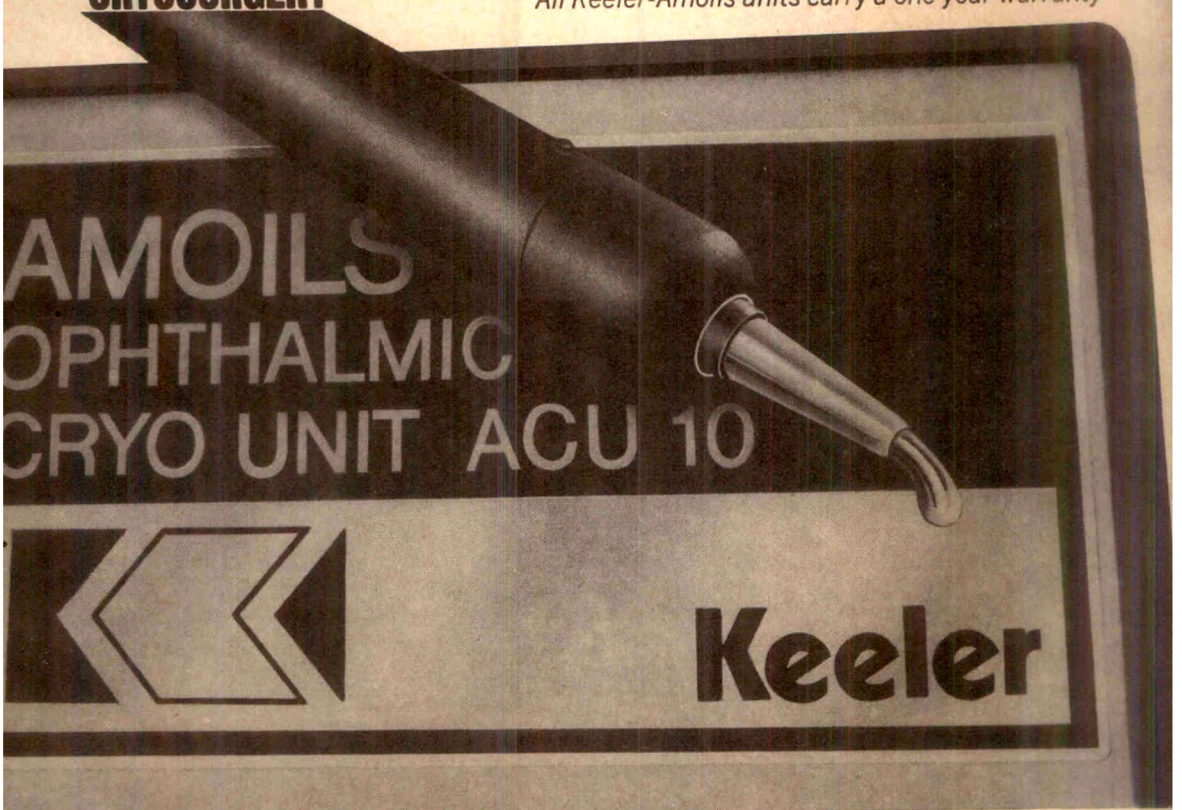
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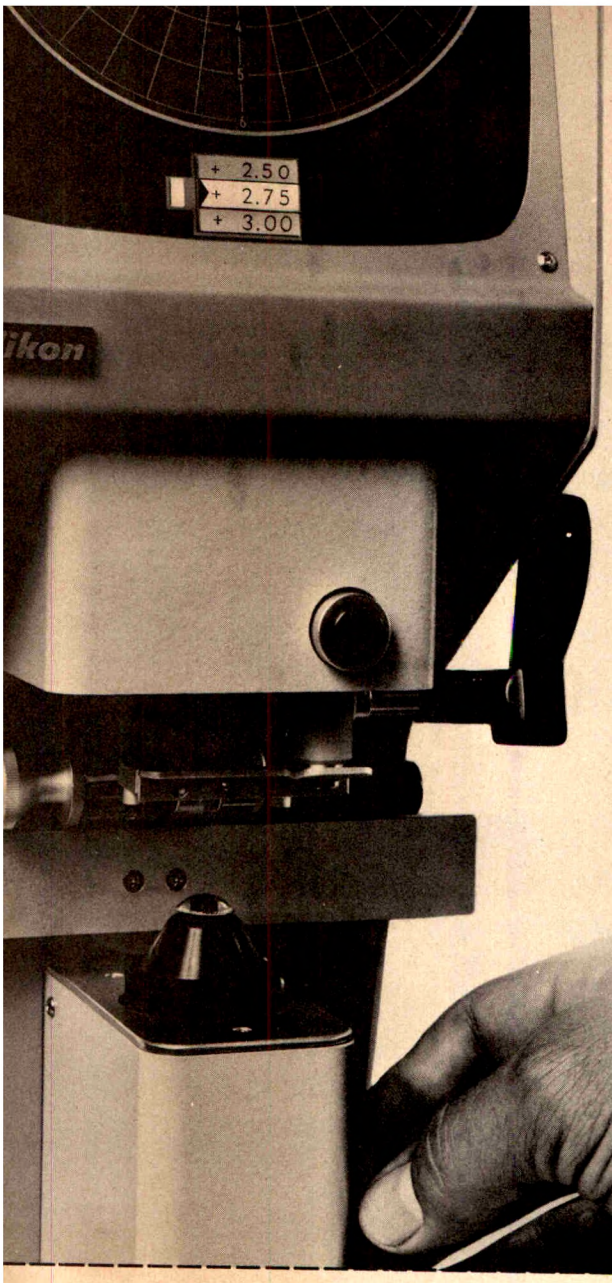
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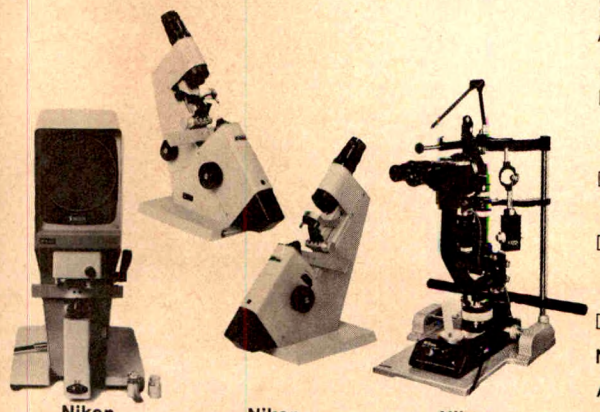
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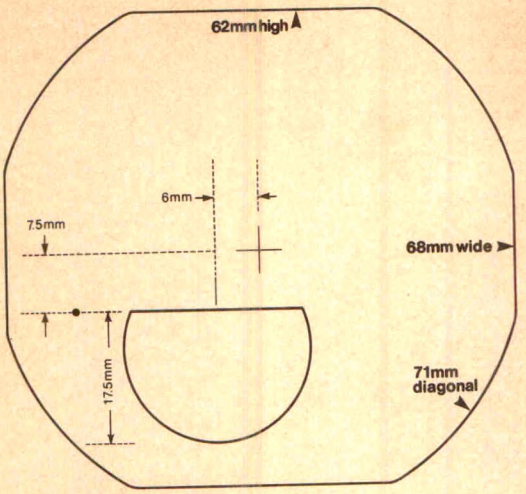
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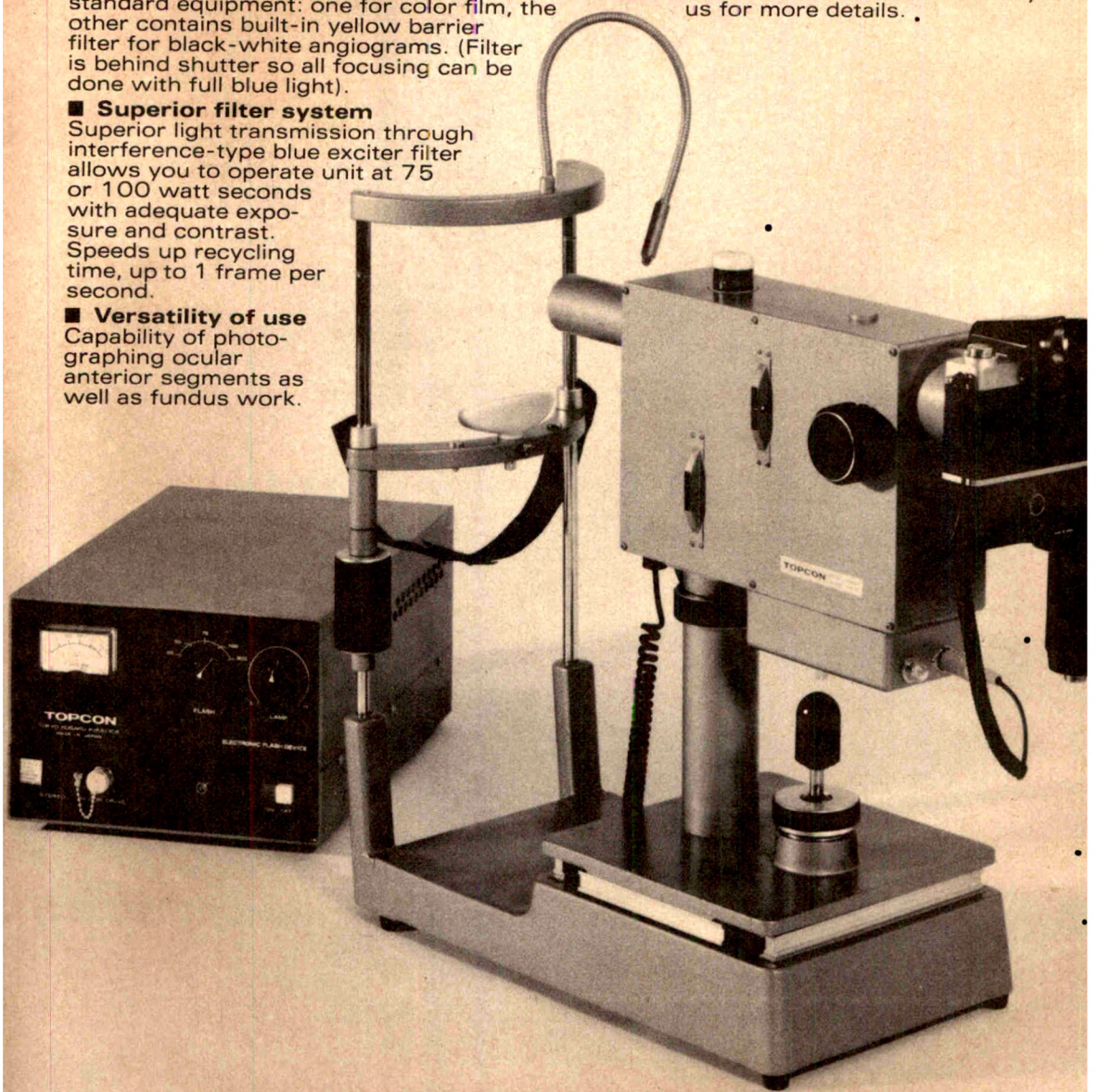
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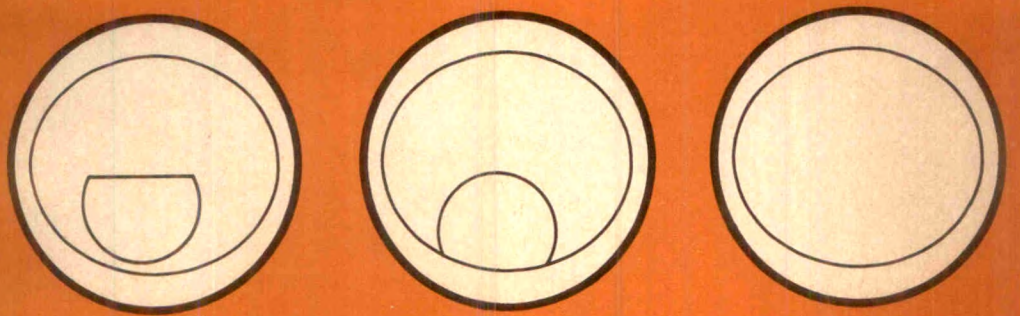
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1. Haas, J. S. and Merrill, D. L.: Amer. J. Ophthal. 54:21, 1962. 2. Linn, M. L. and Jones, L. T.: Amer. J. Ophthal. 65:76, 1968.

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 80 SEPTEMBER, 1975 NUMBER 3, PART II

COMPARATIVE CHANGES IN THE ERROR OF REFRACTION BETWEEN FIXING AND AMBLYOPIC EYES DURING GROWTH AND DEVELOPMENT

CECIL W. LEPARD, M.D.

Grosse Pointe, Michigan

The refractive error of the eye changes progressively from infancy to early adulthood.[1] The hyperopia that exists in most infants at birth tends to increase slightly during the first few years of life,[2-4] followed by a decrease that, during adolescence, may develop into myopia.[2-5]

Brown[3] reported the results of 8,820 observations and computations of the changes in the refraction of one or both eyes of 1,203 persons between birth and middle life (the end of the 51st year). He found an increase in hyperopia of about 1.6 diopters from birth until the age of 7 years, a reduction of nearly 2 diopters in the succeeding eight years, and a further and slower decline during the next 15 years. Similar results were obtained in a later study[4] concerned with the "use-abuse" theory of changes in refractive error in which he showed that a general uniformity of these changes existed during the period of growth (Fig. 1).

In these investigations the eyes were presumably normal with normal visual acuity. Hence, it is not possible to draw conclusions concerning the dependence, if any, on changing error of refraction and the visual acuity. Moreover, in none of the studies was the change in refractive error of one eye compared with that of the other in the same patient, thus eliminating the effect of factors, other than age, on changes in refractive error, for example, heredity in different groups of patients.

To determine the relationship between visual acuity and changes in refractive error with age, and, at the same time, to minimize the influence of other factors that vary from individual to individual and that may influence these changes, I made a retrospective study of the refractive errors of 55 patients with strabismus who had normal vision in one eye and reduced vision in the other.

The patients in the strabismic group had convergent strabismus with a final corrected visual acuity of 0.8 or better in one eye and 0.4 or less in the opposite eye, which had no demonstrable organic disease. I examined them in infancy or early childhood and periodically thereafter through early and late adolescence, and in some cases early adulthood, in order to compare changes in the refractive error of eyes with normal visual acuity and those having partial vision.

A second group of 55 patients without strabismus, in similar age groups, having comparable refractive errors, but with normal corrected visual acuity in both eyes, that is, 0.8 or better, served as a control group.

The refractive errors of the patients at the initial examination in both the strabismic and the control groups are shown in Table 1.

Brown[6] also made repeated measurements of changes in the refractive errors in groups of patients with and without strabismus

From Children's Hospital of Michigan, and Wayne State University, College of Medicine, Detroit, Michigan. This study was supported by a grant from the Bessie Scotten George Fund, Children's Hospital of Michigan, Detroit.

Reprint requests to Cecil W. Lepard, M.D., 413 Fisher Rd., Grosse Pointe, MI 48230.

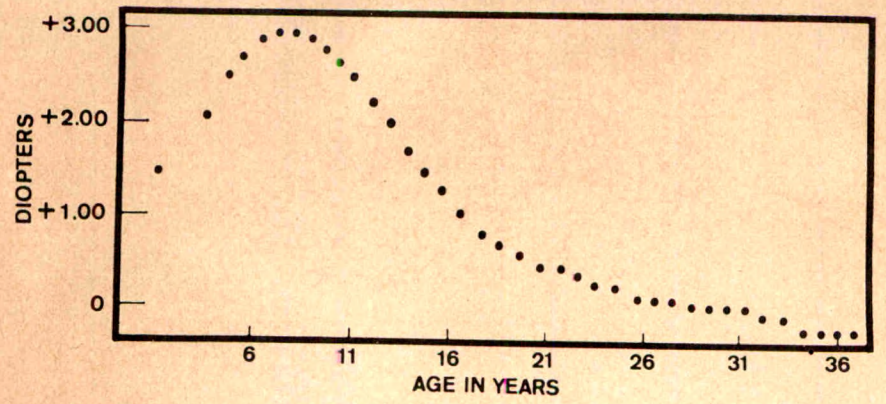


Fig. 1 (Lepard). Refraction curve of changes in 1,737 persons, based on the 1.52 diopters of hypermetropia found in 97 of the eyes before the age of 2 years. (From Brown[4]).

during the first two decades of life, but he did not report visual acuity in either group of patients.

Subjects and methods

All patients in the strabismic group were diagnosed at initial examination as having convergent strabismus. The corrected visual acuity in the fixing eye was 0.8 or better and 0.4 or less in the amblyopic eye, which had not improved over five years or more, either by wearing corrective lenses, or by occluding the fixing eye, with or without orthoptic treatment or surgery. The final corrected visual acuity of the amblyopic eyes is shown in Table 2.

All patients in the control group had less than 4 degrees of esophoria or exophoria and less than 2 degrees of right or left hyperphoria, as measured with the Maddox rod for distance. The corrected visual acuity of each eye was 0.8 or better in all instances.

The age of the patients when first examined is shown in Table 3. The youngest patient in the strabismic group was 6 months old and the oldest, 9 years old. The youngest and oldest in the control group were 7 months old and 9 years old. The average age at first examination was 3.7 years for the strabismic and control groups.

The interval between first and last refraction was never less than five or longer than 29 years (Table 4). The average interval between first and last examination was 14 years for the strabismic group and 13 years for the control group.

TABLE 1

Refractive errors at initial observation

Group	Hyperopic Eyes	Myopic Eyes
Control	88 (7 diopters or less) Average, 1.79 diopters	22 (21, 3 diopters or less) (1, 6 diopters)
Strabismic		
Fixing eyes	48 (9 diopters or less) Average, 3.08 diopters	7 (3 diopters or less)
Amblyopic eyes	46 (9 diopters or less) Average, 3.46 diopters	9 (7, 3 diopters or less) (2, 13 and 15 diopters)

All eyes were refracted under cycloplegia; 0.5 or 1% atropine sulphate was instilled in eyedrop or ointment form to children under 5 years of age, morning, noon, and night on the day before examination and morning and noon on the day of refraction. A solution of 4% homatropine drops was administered three times to patients 5 years of age and older at ten-minute intervals beginning one hour before examination. The same cycloplegia was used repeatedly in the same patients throughout the study.

Spherical and cyclindrical corrections, alone or in combination, were taken into account when determining the error of refraction by adding half the cylindrical correction to the spherical correction.

A Snellen chart was employed to determine final corrected visual acuity with or without cycloplegia, whichever of these resulted in better vision. Only distant visual acuity was considered.

Results

The average refractive errors of all patients in the strabismic group from ages 1 to 28 years are shown in Figure 2. Both the amblyopic and the fixing eyes were approximately 1 diopter more hyperopic from about age 1 to 4 years. After age 7, the fixing eyes were more myopic, in contrast to the amblyopic eyes that had not changed significantly; these differences in behavior of the two eyes result in a significant disparity in the refractive errors of the two eyes from age 13 onward. The average refractive error in the amblyopic eyes of those patients when last examined is essentially the same as when first examined (Fig. 2 and Table 5). Thus, there is no apparent trend in the refractive error of the amblyopic eyes for more than 25 years, whereas the average change in the eyes of the same patient with normal visual acuity is about 3 diopters, a value essentially identical with that observed in the two eyes of all patients in the control group (Table 5).

TABLE 2

FINAL CORRECTED VISUAL ACUITY OF 55 AMBLYOPIC EYES

Visual Acuity				
0.4	0.3	0.2	0.1	<0.1
No. of Eyes				
17	6	7	14	11

TABLE 3

DISTRIBUTION OF PATIENTS BY AGE AT INITIAL EXAMINATION

Age, yrs				
0–1	1–2	2–4	4–6	6–9
Control Group				
6	4	17	18	10
Strabismic Group				
5	10	10	19	11

TABLE 4

DISTRIBUTION OF PATIENTS WITH RESPECT TO INTERVAL BETWEEN FIRST AND LAST REFRACTION

Age, yrs			
5–8	9–10	11–20	20–29
Control Group			
16	6	21	12
Strabismic Group			
11	7	32	5

TABLE 5

AVERAGE CHANGE IN ERROR OF REFRACTION BETWEEN FIRST AND LAST EXAMINATION*

Control Group	
RE	LE
-2.50 ± 1.92†	-2.48 ± 1.92
Strabismic Group	
Fixing Eye	Amblyopic Eye
-2.35 ± 1.93	-0.47 ± 1.70

* 55 patients in each group.
† Standard deviation.

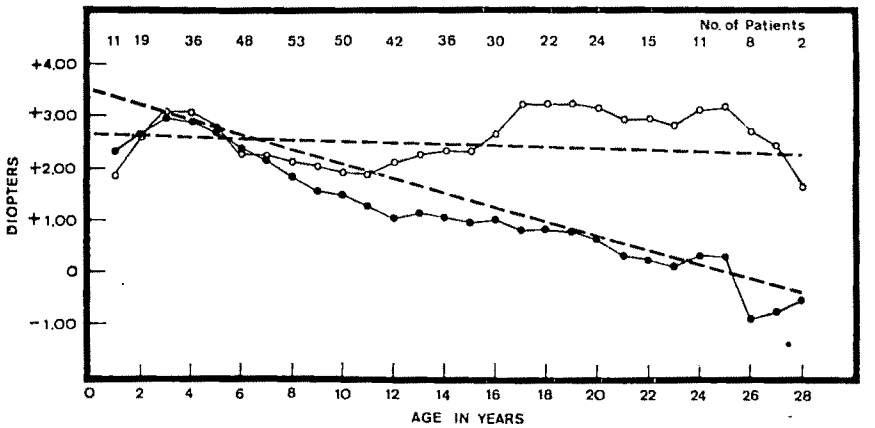


Fig. 2 (Lepard). Solid lines show the average refractive error of the fixing (closed circles) and amblyopic (open circles) eyes of 55 patients (797 examinations) with growth and development at yearly intervals. (In those patients where the interval between examinations exceeded one year, the refractive error was estimated by interpolation.) Broken lines are least squares fits to all of the observed refractive errors in each group of patients. The numbers at the top show the number of patients seen at any one age.

Discussion

These data indicate that eyes with normal visual acuity become progressively more myopic with growth and development until 25 years of age and are in excellent agreement with the data of Brown[4] (Fig. 1), whereas contralateral eyes with impaired acuity show no significant change in the average refractive error during the same period (Fig. 2).

Calculations based on the Student's *t*-test indicate that the slope of the regression line (broken lines, Fig. 2) pertaining to the eyes with impaired vision (amblyopic eyes) is not significantly different from zero at a level $P = 1.0$. The slope of the regression line pertaining to the eyes with normal vision (fixing eyes) is dependent on age. These calculations indicate that there is less than one chance in a million that the differences in the refractive errors in the two groups of eyes would occur by chance.

There is thus a real difference in the change in the average refractive error that occurs with growth and development in the amblyopic and the fixing eye of the same patient. While the average change in refractive error of the amblyopic eyes is essen tially nil, nevertheless, only nine of the eye did not change with age and about two third became more myopic with age, albeit to lesser degree than the eyes with norma visual acuity; these changes were balance by those of 13 eyes that were more hyperopi with time. The changes in the eyes wit reduced visual acuity are more normall distributed than those with good vision, a seen from the curves (Fig. 3) showing dis tribution of the refractive error in the tw groups of eyes.

The average change in the refractiv errors of both eyes in the control group i similar to that of the eyes with normal visio in the strabismic group and there is little vari ation between the change in the two eyes o the same patient, that is, the difference wa 1 diopter or less in 54 of the 55 patient The difference between the two eyes in th strabismic group was greater than 1 diopte in 37 of the 55 patients, ten being greate than 3 diopters and two being greater tha 5 diopters. The changes in the refractiv errors of the amblyopic eyes did not paralle those of the eyes with normal visual acuit

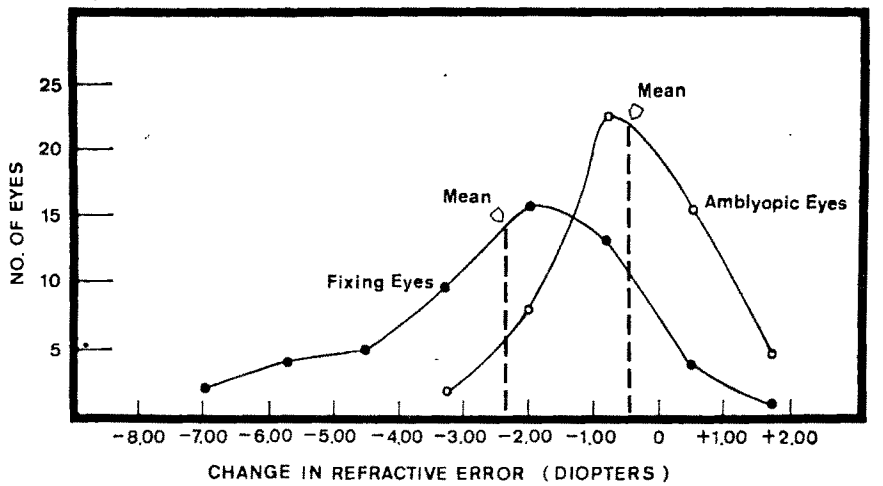


Fig. 3 (Lepard). Distribution of changes in refractive error of normal (fixing) and impaired (amblyopic) eyes of 55 strabismic patients between initial (average 3.7 years) and final (average 17.7 years) examination.

n most instances.

It is not possible to compare directly the esults of the present study with those of Brown[6] who also measured changes in refractive error in a group of strabismic patients, because he did not state whether his patients were amblyopic or report the changes in each eye separately. Even if we assume that some of the eyes had reduced visual acuity due to amblyopia, his results would be comparable only with an average of the amblyopic and fixing eyes of the group of strabismic patients reported in this study.

Finally, my results lend support to the use-abuse theory of changes in refraction that holds that myopia increases during the early school years as a result of use or abuse of the eyes, or both, as opposed to the biologic theory that emphasizes the role of growth and heredity as a causative factor of refractive changes in youth. Heredity is clearly the same in the amblyopic and the fixing eyes but, nevertheless, significant refractive changes were observed only in the better functioning eye. However, in accord with Brown, I do not feel available evidence in support of this theory outweighs that against it, so it is premature to debate the mechanism by which use or abuse, or both, could result in refractive changes.

Summary

Measurements of the refractive errors in 55 strabismic patients—one eye with visual acuity of 0.8 or better and the other with reduced vision, 0.4 or less due to amblyopia, and performed at roughly two-year intervals during growth and development to approximately age 25 years—showed that the eye with normal visual acuity was significantly more myopic with age, whereas there was no appreciable change in the average refractive error of the amblyopic eye.

Both eyes of a control group of patients of similar age having normal distant vision and orthophoria were more myopic with age. In this group there was an insignificant difference in the change in refractive error of one eye compared with its fellow during comparable periods of time.

Acknowledgment

Professor Harvey J. Arnold provided assistance in the statistical aspects of this study.

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Ophthalmic miniature

This precision of observation, this exactness in the noting of detail of the diverse aspects of a personage, an animal, an object, a deformity, an infirmity, are to be found again and again in the most unexpected areas. A doctor, Tony Michel Torrillon, has observed that the cripples and the sick who appear in Brueghel's paintings have been drawn with such precision that a doctor today can still diagnose their disease. Such is the perfect type of Burger's disease that we find in "The Battle of Carnival and Lent," where we also see a syphilitic tabes. In "The Beggars," one of the five is afflicted with spastic paraplegia. "The Wedding Feast" gives examples of opposite types of thyroid disturbances: a myxoedema and a case of Basedow's Disease. The painting of "The Blind" presents five different cases of blindness, all readily identifiable by specialists, namely: (1) Pemphigus blindness; (2) Atrophy of the eyeballs; (3) Corneal leukoma; (4) Amaurosis; (5) Enucleation.

Claessens and Rousseau,
Our Brueghel

IMMUNOLOGIC STUDY OF NONSYPHILITIC INTERSTITIAL KERATITIS WITH VESTIBULOAUDITORY SYMPTOMS

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In 1945,[1] one of us (D.G.C.) described a clinical entity consisting of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. Since 1945, several authors[2-8] have discussed the possibility that this entity was a facet of systemic vasculitis. Eight patients with this syndrome have had aortitis or generalized vasculitis diagnosed by biopsy or necropsy,[2,9-13] and 11 patients have had a clinical course consistent with systemic vasculitis.[14-20] We are aware of two other patients with this entity who died of aortitis (unpublished data).

The symptoms, physical findings, and clinical course in the syndrome of nonsyphilitic interstitial keratitis with vestibuloauditory symptoms have been described.[1-20] Patients and their parents have uniformly negative serologies for syphilis. Positive laboratory findings have included mild leukocytosis (50% of cases), mild eosinophilia (27%), and elevated sedimentation rates (21%). Extensive investigation for a viral, bacterial, or parasitic etiology has given negative results.

There is increasing evidence that some patients with systemic collagen diseases have an altered cell-mediated immune response.[21-23] We investigated the immunologic status of four patients with nonsyphilitic interstitial keratitis with vestibuloauditory symptoms to determine whether immunologic abnormalities are involved in the pathophysiology of this disease.

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SUBJECTS AND METHODS

The four patients with nonsyphilitic interstitial keratitis with vestibuloauditory symptoms were nulliparous white women, aged 17 to 55 years, with a mean age of 30 years.

One patient (Case 1)[1] had ghost vessels in the posterior corneal stroma, total nerve deafness, and recurrent symptoms of bilateral external ocular irritation. Another patient (Case 2) had bilateral nerve deafness and had recurrent exacerbations of her interstitial keratitis requiring topical corticosteroids. The third patient (Case 3) had inactive interstitial keratitis with a minimal auditory function that was controlled with systemic corticosteroids. One patient (Case 4) had total nerve deafness and old interstitial keratitis. No patient had signs or symptoms of an ongoing allergic vasculitis. We provided a written and oral explanation of the experimental protocol and obtained informed consent. All blood specimens were coded so that the technicians performing the assays were not aware of the diagnoses. The control subjects were age-matched blood bank volunteers with no known ocular or systemic disease.

All subjects were tested with a routine battery of laboratory tests used in evaluating patients suspected of having immunologic abnormalities, in addition to HL-A typing and experimental assays of cell-mediated immunity.

Using standard laboratory methods, we performed the following tests: urinalysis, complete blood cell counts (CBC), eosinophil counts, erythrocyte sedimentation rates,

fluorescent treponemal antibody (FTA), VDRL syphilis serology, rheumatoid factor, lupus erythematosus (LE) preparation, Australia antigen and antibody, alpha-fetoglobulin, antithyroid antibody, antinuclear antibody, cryoglobulins, direct and indirect Coombs' test, total complement levels, and quantitative immunoglobulin levels.

The HL-A typing was done with the microdroplet lymphocyte cytotoxicity test.[24] The percentage of "thymus derived lymphocytes" in the subjects' peripheral blood was determined by Rosette tests, using Wybran and Fudenberg's methodology.[25] Lymphocyte mitogen stimulation with phytohemagglutinin was done using a modification of the technique of Hartzman and associates.[26] A leukocyte migration inhibition (LMI) assay was performed using a 3M soluble potassium chloride extract of pooled allogenic normal cornea,[27] in an LMI technique we previously described.[28]

Results

We observed normal values in the patients in the following laboratory assays: urinalysis, VDRL, FTA, alpha-fetoglobulin, antinuclear antibodies, CBC, total complement levels, quantitative immunoglobulins, antithyroid antibody, direct and indirect Coombs', rheumatoid factor, LE preparation, cryoglobulins, and Australian antigen and antibody.

Three patients (Cases 2, 3, and 4) had elevated erythrocyte sedimentation rates. Three patients (Cases 1, 2, and 4) had W-17, a second-segregant series histocompatibility antigen that occurs in 3 to 10% of the normal population.[29,30] All four patients had a statistically significant (Student's *t*-test) migration inhibition factor index against normal allogenic pooled cornea that was greater than the randomly selected normal volunteers.

Discussion

Approximately 25% of patients with this syndrome have had clinical or tissue findings consistent with a polyarteritis nodosa-like condition.[2,3,9,10,17] Many authors have postulated that immunologic derangements play an important role in the pathophysiology of the vasculitis syndromes, although human experimental evidence has not been impressive.[21,31] In related connective tissue disorders, there is increasing evidence that there is altered cell-mediated immunity.[21,32,33]

There has been no evidence of an altered humoral immunity in patients with this disorder.[2,8,13] In the present study we detected no abnormalities in the levels of immunoglobulins, nor did any of the patients have positive LE preparations, antinuclear antibodies, antithyroid antibodies, cryoglobulins, or abnormal complement levels. Since positive Australian antigen and antibodies had been reported in some patients with polyarteritis nodosa,[34] these were also measured in our patients, and none were detected. While some collagen vascular diseases have characteristic alterations in these general tests of humoral immune status,[35] it would appear that patients with this syndrome and patients with polyarteritis nodosa do not. Since our patients were not tested for specific antibodies against cornea and cochlea, disorders of humoral immunity cannot be ruled out, although they are unlikely.

Since this clinical entity is rare, we were unable to gather a sufficient number of patients to reach statistically significant conclusions, although the results of an LMI assay using normal pooled allogenic cornea as an antigen and the HL-A typing of these patients were interesting.

In some animal systems, the immune-response genes that are responsible for the development of cellular immune response are linked to the histocompatibility antigens.[36] There is increasing evidence of a correlation between HL-A antigen types and some of the collagen vascular diseases.[30,36] While the number of patients we tested is too small for significant results, three of the four patients (75%) had W-17, a second-segregant series histocompatibility antigen that

occurs in 3 to 10% of the normal population.

All of the patients had increased cell-mediated immunity toward normal allogenic corneal antigen as compared with normal control subjects, suggesting that possibly cell-mediated immunity to cornea may play a role in the pathophysiology of nonsyphilitic interstitial keratitis. However, it is possible that any corneal inflammation leads to cell-mediated immunity to corneal antigens.[37]

The normal values obtained in lymphocyte stimulation with phytohemagglutinin and in the thymus-derived rosette-forming cell assay indicate that there does not appear to be a generalized alteration in the cell-mediated immunologic function in these patients.

Summary

We studied four patients with the clinical entity of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms to determine whether immunologic abnormalities play a role in its pathophysiology. There was no evidence of alteration in nonspecific cell-mediated or humoral immunologic status of any of the patients studied. Three of the four patients had W-17, a histocompatibility antigen that occurs in 3 to 10% of the normal population. All four patients had increased cell-mediated immunity against normal allogenic corneal antigens compared to normal control subjects. There seems to be no apparent generalized alteration of the immune system in this syndrome.

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CLINICAL EVALUATION OF ADENINE ARABINOSIDE AND IDOXURIDINE IN THE TREATMENT OF OCULAR HERPES SIMPLEX

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In the 15 years since Kaufman and coworkers[1,2] introduced idoxuridine (IDU), our understanding of the multifaceted nature of ocular herpes simplex has reached levels of sophistication sufficient to make the therapeutic limitations of this drug all too apparent. Ocular herpes is not simply an infectious epithelial process for which IDU is usually adequate, but one that may involve trophic healing problems, immune reactions requiring corticosteroids, and chronic recurrence. As more patients with simple and complicated infections are using IDU, the problems of true allergic reaction to the drug, toxic keratoconjunctivitis, and clinical IDU-resistance have made the need for alternative antivirals paramount. Unfortunately, the majority of new agents investigated—5-methyl-amino-2′-deoxyuridine (MADU), Poly I-C, and cystosine arabinoside—are either too weak or too toxic therapeutically to merit clinical trials, while other more promising drugs, such as trifluorothymidine (F_3T), have yet to undergo extensive clinical testing.[3-7]

Recently, attention has focused on one agent that appears to fulfill the criteria for therapeutic efficacy and lack of toxicity. Adenine arabinoside or ara-A (VIRA, 9-β-arabinofuranosyladenine) is an antimetabolite purine analog obtained from the fermentation filtrates of *Streptomyces antibioticus* and demonstrated in vitro to have broad-spectrum anti-DNA viral activity against herpes simplex, cytomegalovirus, simian herpes vaccinia, and varicella. It was synthesized as an anticancer agent in 1960[8] and in 1968.[9,10]

In early animal studies, Kaufman, Ellison, and Townsend[11] reported good therapeutic results in treating experimental herpetic uveitis with subconjunctival injections of 5% ara-A suspension. The first clinical investigations[12] were double-blind and showed that ara-A was therapeutically as effective as IDU in epithelial herpes, and of as little use as IDU in treating adenoviral infections. Additionally, because Hyndiuk and associates[13] favorably demonstrated the superiority of ara-A over IDU in experimental vaccinial keratitis in rabbits, one of our[12] patients with bilateral vaccinial blepharoconjunctivitis was treated double-blind with IDU in one eye and ara-A in the other. The therapeutic response was more rapid in the ara-A-treated eye although both resolved well within ten days. In this same series,[12,13] three patients with herpes and known severe IDU allergy used ara-A successfully without any side effects, and an apparent favorable effect was noted on treating uveitis. This latter observation led to studies[14] on the intraocular penetration of ara-A and IDU in rabbits and humans, revealing that metabolites, not the parent compounds, enter the eye. The IDU is dehalogenated to deoxyuridine, a biologically inactive compound, while ara-A is deaminated to hypoxanthine arabinoside, a more soluble compound that possesses 20% more of the antiviral activity of both IDU and ara-A.[15] The penetration of this weaker but still active antiviral drug by aqueous humor was responsible for the favorable

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Presented at the ara-A Symposium, San Francisco, California, Sept. 17, 1974.

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therapeutic effects on herpetic uveitis. Systemically applied ara-A in humans with herpetic uveitis is being investigated; preliminary results are encouraging.[16] Additional double-blind toxicity studies with reference to corneal, epithelial, and stromal wound healing demonstrated appreciable epithelial toxicity with IDU therapy and no toxicity with ara-A therapy. Stromal wound strength was equally impaired (40%) by both antimetabolites.[17]

Because of the favorable results in this earlier work, I investigated the value of ara-A in treating infectious epithelial herpes in a double-blind study using IDU and in an open-drug study that included patients known to be intolerant of IDU because of toxicity, allergy, or resistance to IDU therapy. I observed 112 patients with active epithelial herpes.

Patients and methods

The patients, selected from the clinics and corneal consultation services, underwent history and clinical examination including visual acuity, intraocular pressure (tactile pretreatment, applanation tonometry after treatment), and slit-lamp biomicroscopy with particular attention to the status of the lacrimal puncta, conjunctiva, corneal epithelium, stroma, anterior chamber, iris, and lens. A dilated ophthalmoscopic examination was performed at the beginning and end of the study. Only patients with dendritic (85 eyes), dendrogeographic (12 eyes), or geographic (15 eyes) ulcers were included in the study. The diagnoses of the first 36 patients were confirmed by positive viral cultures on human embryonic kidney, and the first 80 patients were evaluated for potential ara-A systemic side effects by obtaining a complete blood cell count, platelet count, serum glutamic oxalopyruvic transaminase, serum alkaline phosphatase, serum bilirubin, blood urea nitrogen, and fasting blood glucose at the beginning and end of the therapeutic period, or monthly for those receiving long-term therapy.

Double-blind study—The 54 patients in the double-blind group received no antiviral therapy for at least 30 days before the study. The mean duration of symptoms before therapy in the ara-A-treated group was 9.5 days for 21 patients; seven patients were symptomatic for more than one month (average, 2.2 months). In the IDU-treated group, 23 patients had prestudy symptoms for approximately 7.4 days; six patients had symptoms for approximately 1.8 months. We measured the size of the epithelial ulcers in square millimeters in 23 patients to compare the average size of lesions in each group with the average time of complete reepithelialization (Table 1). Narrow linear branching dendrites were 0.1 mm wide. Dendrogeographic and geographic ulcers were measured at their widest dimensions and the area was calculated accordingly. The 54 patients placed on a randomly assigned regimen received either coded 3.0% ara-A ointment or 0.5% IDU ointment, five times daily. No change was made in the corticosteroid therapy of the 16 patients who had been receiving these drugs but all eyes received topical antibiotics and eyes with stromal disease (15) or uveitis (8) were dilated. Clinical observations were made on every patient on day 3, 5, or 7 after initiation of therapy, and once or twice weekly thereafter. I asked all patients for their personal assessment of drug tolerance at each visit.

Open-drug study—The 58 patients in the open-drug study group either had known severe allergy (ten patients) or toxic reaction (11 patients, five with punctal occlusion) to IDU, or had no improvement or deterioration of ulcers while receiving IDU therapy (37 patients) and were considered clinically resistant. Of these clinically resistant patients, 26 had received IDU for approximately 12.5 days, and 11 for approximately 8.1 months. This last figure was distorted, however, since one patient had received IDU for 756 consecutive days. The IDU was discontinued and all 58 patients received 3% ara-A ointment, five

TABLE 1

DOUBLE-BLIND THERAPY OF EPITHELIAL HERPES SIMPLEX

	ara-A	IDU
Diagnosis		
Dendritic ulcer	21	19
Dendrogeographic ulcer	4	5
Geographic ulcer	3	2
Total	28	26
Mean time to complete healing (range)	12.4 days (2–22), 27 eyes	11.5 days (2–43), 24 eyes
Mean area of ulcers and time to complete healing	12.2 mm^2, 11.2 days, 12 eyes	13.7 mm^2, 11.8 days, 11 eyes
Mean duration of therapy to complete healing (range)	25 days (7–73 days)	20 days (9–98 days)
Dropped from study (trophic ulcers)	1	2
Visual acuity after therapy		
Improved	11 (64%)	4 (30%)
Unchanged	6 (35%)	8 (63%)
Worse	0	1 (7%)
Adverse drug reactions	3 mild	2 moderate 2 severe

times daily. Twenty-two of these patients were already receiving corticosteroids. Six patients were immediately and successfully taken off corticosteroids. Ten patients not initially receiving corticosteroids in the present study, and who had received them previously, were placed on corticosteroid therapy to control stromal edema or uveitis. Sixteen patients were maintained on their prestudy corticosteroid therapy. All 58 patients received topical antibiotics, 31 were maintained on mydriatics, and six on antiglaucoma drugs. They were followed clinically as described in the double-blind study. Initial ulcer size was measured in 25 patients (Table 2).

RESULTS

Double-blind study—Twenty-eight patients received ara-A and 26 received IDU. The average age of patients receiving ara-A was 50.3 years, ranging from 2 to 73 years. The average age of patients receiving IDU was 50.5 years, ranging from 21 to 85 years. Eighteen males and ten females received ara-A, and nine males and 17 females, IDU. In the ara-A group, 21 patients had had previous herpes while only 11 of the IDU patients were having a recurrence.

The mean time to complete reepithelialization was 12.4 days for ara-A-treated eyes (two- to 22-day range) and 11.5 days for IDU-treated eyes (two- to 43-day range) ($P > .05$). One patient in the ara-A group and two in the IDU group were not included in the efficacy analysis because their lesions became trophic and soft contact lens therapy was instituted.

The mean area of the ulcers in the 12 ara-A-treated eyes was 12.2 mm^2 with a mean healing time of 11.2 days, and 13.7 mm^2 for 11 IDU-treated eyes with the mean healing time of 11.8 days ($P > .05$). The mean duration of therapy for ara-A-treated eyes was 25 days (seven to 73 days) and 20 days (nine to 98 days) for IDU-treated eyes.

Visual acuity after treatment with ara-A was improved in 11 patients (65%) and unchanged in six (35%), while in IDU-treated eyes it was improved in four (30%), unchanged in eight (63%), and worse in one (7%). The better quality vision in ara-A-treated patients was due to smoother epithelial healing rather than to any differences in stromal scarring between the two groups. No patients had or developed elevated intraocular pressures during the study.

TABLE 2

RESULTS OF OPEN-DRUG ARA-A THERAPY OF IDU-INTOLERANT OR RESISTANT OCULAR HERPES

Diagnosis	
Dendritic ulcer	45
Dendrogeographic ulcer	3
Geographic ulcer	10
Total	58 eyes
Mean time to complete healing (range)	10.6 days (2–24), 49 of 57 eyes
Mean pretherapy area of ulcers and time to complete healing (range)*	
Dendritic ulcer	15 eyes, 17.4 mm², 9.3 days (2–24)
Dendrogeographic ulcer	1 eye, 8.5 mm², 15.0 days (15)
Geographic ulcer	5 eyes, 32.3 mm², 15.8 days (8–24)
Duration of ara-A therapy to completely healed eyes (range)	41.5 days (7–192 days), 49 eyes
Dropped from study	
Trophic ulcer†	8
Nonulcerative toxic keratitis	1
Visual acuity after therapy	
Improved	31 (64%)
Unchanged	16 (30%)
Decreased	2 (6%)
Adverse reaction to ara-A (Superficial punctate keratitis)	1 mild

* One dendrogeographic and three geographic ulcers healed only after soft lens therapy; healing time not included in these figures.

† Includes four ulcers from size-measured group.

Subjective and objective evaluation of patient tolerance revealed that in the ara-A-treated group, three patients complained of mild itching or irritation which they felt was drug related. In the IDU-treated group, two patients had moderate redness and tearing and two had severe follicular allergic blepharodermatitis (Fig. 1). The four patients adversely affected by IDU had had previous exposure to the drug and presumably were sensitized.[7]



Fig. 1 (Pavan-Langston). Severe IDU-allergic blepharodermatitis.

Open-drug study—The mean age of patients in this group was 47.3 years (2- to 83-year-old range): 32 patients were male and 26, female. Of the 58 patients in the open-drug study group, 42 had had ocular herpes previously.

The mean time to complete reepithelialization after instituting ara-A therapy was 10.6 days (two- to 24-day range) for 49 of 57 patients included in the efficacy analysis. Eighteen patients did not respond to chemotherapy and ultimately healed with soft lens wear. The diagnosis in these patients was changed to trophic postinfectious ulceration (metaherpes). One patient was not included in the efficacy analysis because his cornea showed only extensive superficial punctate keratitis. As he was receiving IDU at the time of initial examination, chemical toxicity could not be distinguished from herpetic epitheliitis.

The initial size of the ulcers in 25 pa-

tients had been measured and the time of complete healing by size and configuration was determined. Fifteen eyes had dendritic ulcers with a mean area of 17.4 mm² that reepithelialized completely in approximately 9.3 days (two- to 24-day range); the dendrogeographic ulcer in one of two eyes measured 8.5 mm² and healed in 15 days. The other eye did not respond to chemotherapy. Five of eight eyes with geographic ulcers with a mean size of 32.3 mm² (4.5 to 72 mm² range) healed in approximately 15.8 days. The remaining three eyes did not respond to chemotherapy and, as with the chemotherapeutically nonresponsive dendrogeographic ulcer, were transferred to the trophic ulcer group and healed with soft contact lens therapy.

The mean time to complete healing for ara-A-treated eyes was 41.5 days (seven- to 192-day range). This somewhat extended therapeutic course was due to 16 patients using ara-A as a prophylactic cover while corticosteroids were being tapered.

Visual acuity after treatment was improved in 31 patients (64%), unchanged in 16 (28%), and worse in two (6%). Two of three patients who entered the study with elevated intraocular pressures had been receiving topical corticosteroids. Two other patients were placed on corticosteroid therapy and antiglaucoma medication simultaneously (study days 7 and 22) to treat uveitis with elevated intraocular pressure. A sixth patient started topical corticosteroids on study day 8, developed elevated pressures on day 22, and was appropriately treated. Only two patients continued to receive antiglaucoma medication after other ophthalmoscopic medications were discontinued.

Only one of the 58 patients treated reported adverse experiences. He complained of mild to moderate redness and irritation, attributed to the drug, and had punctate keratitis. Ara-A was discontinued after nine days of therapy by which time his ulcer had healed. No patients developed punctal occlusion. The IDU-toxic occluded puncta of five patients entering the study opened spontaneously after two to four months of follow-up.

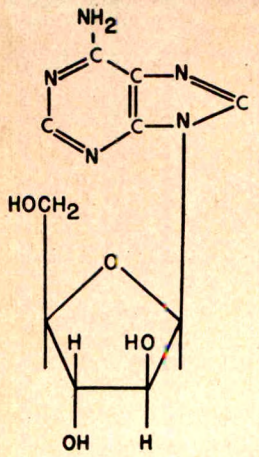
Laboratory tests—All hematologic, renal, and hepatic function tests before and after treatment were unchanged and showed no adverse systemic side effects from ara-A.

Discussion

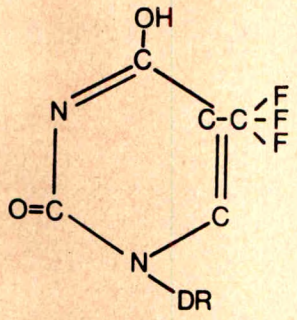
The present chemotherapeutic approach to ocular herpes using IDU has clinical failure rates that have been as high as 27 and 39.5%.[7,18] In the past these failures were attributed to patient neglect of medication schedules, inadequate drug levels because of poor solubility, and rapid in situ metabolism. These factors are now being implicated less frequently and there are more patients with herpes resistant to or intolerant of the only commercially available, effective antiviral medication, IDU.

The present study was divided into double-blind and open-drug groups because I wanted to establish ara-A's efficacy against the IDU prototype, and because many of our patients with chronic recurrent herpes needed antiviral medication but were either not helped or often hurt by repeated exposure to IDU. These patients included not only those in the present study but more than 40 others receiving corticosteroid therapy for stromal keratitis, with ara-A used as a prophylactic umbrella, and 25 patients with penetrating keratoplasty who benefited from ara-A's relative lack of epithelial toxicity.

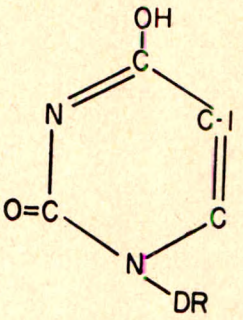
In the current double-blind study, these data show no significant difference in the time of complete epithelial healing ($P > .05$). This confirms observations made in earlier animal and human studies comparing these two drugs.[11,13] There was also no significant difference in the size of the ulcers (13.7 mm² vs. 12.2 mm²) to prejudice the results in favor of one drug ($P > .05$). The average healing time in this study is somewhat longer than that reported by Patterson and Jones[18]



9-β-D-ARABINOFURANOSYLADENINE
(ara-A)



TRIFLUOROTHYMIDINE
(F_3T)



IDOXURIDINE
(IDU)

Fig. 2 (Pavan-Langston). Comparative molecular structures of ara-A, F_3T, and IDU.

(7.5 days), and by Wellings and associates[7] (8.2 days). As the initial size of the ulcers in the latter study and the present one were almost identical if expressed as 0.1 mm², this disparity may reflect many more chronically damaged corneas in the present study that would predispose to slower healing, or simply the disparity among multicenter studies.

In the open-drug study, 58 patients who, for reasons of allergy, toxicity, or resistance, could not use IDU, tolerated ara-A therapy extremely well; the disease of 49 of these patients resolved with the latter therapy. Although the average ulcer size in these patients was larger than that in the double-blind group, the average healing time was significantly less (10.6 days vs. 11.4 days for IDU and 12.5 days for ara-A, $P < .05$). This may partly reflect IDU-toxic interference with healing in certain sensitized patients and partly the effect of switching from a pyrimidine antimetabolite, to which the virus may be clinically resistant, to a purine analogue that has a totally different molecular structure (Fig. 2). No patient became sensitized to ara-A during the course of study and more than 14 patients have received ara-A for 1½ years (11 without difficulty and three with a mild superficial punctate keratitis).

The molecular structure of ara-A and its

lack of any halogen molecule may be an advantage over another promising antiviral, F_3T, which is less toxic than and superior to IDU in short-term treatment of epithelial herpes and possibly in uveitis. Structurally, however, it differs from IDU only in the replacement of a single iodine molecule by three fluoride molecules. Fluoride is notoriously more toxic than iodine and patients sensitized to the basic nucleoside of IDU might be expected to be sensitive to F_3T. One patient in the present study had received F_3T because of a severe IDU allergy. Within two weeks she developed a similar allergy to F_3T. Subsequent ara-A therapy extending over a three-month period resulted in corneal epithelial healing and no adverse drug reaction. In a more extensive study comparing F_3T, ara-A, and IDU, however, Jones and associates[19] noted no cross-sensitivity among any of these drugs. Wellings and associates[7] stated that "F_3T appears to be less toxic for the human cornea than IDU but this can be fully assessed only in a large series of cases treated for longer periods than in the present study" (14 days).

Ara-A is chemotherapeutically equal to IDU in the treatment of routine epithelial herpes but clearly superior in treating recurrent disease in patients intolerant of or resistant to IDU. There is no cross-allergenicity and no patients displayed significant toxic reactions after 192 days of continuous ara-A use.

Summary

A double-blind clinical study comparing idoxuridine (IDU) with adenine arabinoside (ara-A) in treating 54 routine herpetic ulcers, and an open ara-A therapy study of 58 herpetic ulcers in patients intolerant of or resistant to IDU, was carried out over a four-year period. There was no significant difference in healing time between IDU-treated eyes (11.5 days) and ara-A-treated eyes (12.4 days) in the double-blind study but there were four moderate to marked adverse reactions to IDU and only two mild reactions to ara-A. In the open-drug study 21 patients who were intolerant of IDU because of allergy or toxicity and 37 patients who had ulcers resistant to or deteriorating on IDU therapy used ara-A up to 192 days without any adverse reaction. Mean healing time was 10.6 days for 49 of 57 patients in the efficacy analysis. Eight patients developed trophic ulcers that responded to soft lens therapy and one was dropped from the study because his initial disease could not be distinguished from severe IDU-induced keratitis.

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OPHTHALMIC MINIATURE

Per contra: The converse of secundum quid is drawing a conclusion about an individual on the basis of the general characteristics of the group to which he belongs or by arguing that the properties of a whole are also the properties of each part.

"I-I'm a little girl," said Alice . . . "A likely story indeed!" said the Pigeon in a tone of deepest contempt. "I've seen a good many little girls in my time, but never one with a neck like that!"

Dwight J. Ingle
Fallacies and errors in the Wonderlands
of Biology, Medicine, and Lewis Carroll
Perspectives in Biology and Medicine
15:258, 1972

CONJUNCTIVAL SQUAMOUS CELL CARCINOMA COMBINED WITH MALIGNANT LYMPHOMA

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Fort Sam Houston, Texas

Squamous cell carcinoma of the conjunctiva, a rare disease, predominantly affects elderly men[1-6]; it is especially rare among whites in industrialized countries. Younger patients with the disease almost invariably reside in tropical countries and are nonwhite.[7-10]

Our case occurring in a 36-year-old white woman with malignant lymphoma and squamous cell carcinoma of the conjunctiva highlights the unanswered questions regarding the etiology of the tumor.

CASE REPORT

A 31-year-old white woman in September 1969 had poorly differentiated, nodular malignant lymphoma, based on findings of a lymph node biopsy and staging laparotomy, after symptoms and lymphadenopathy of one year's duration.

In December 1969, neoplastic cells were noted on a bone marrow examination, and she was begun on a chemotherapeutic regimen in accordance with the Southwest Tumor Group Protocol.

In September 1970, the treatment was altered because of side effects; the new regimen was continued until December when she was in complete remission.

Because of new symptoms in January 1971, a third form of chemotherapy was instituted until her deteriorating status required numerous combinations of various drugs in February 1972. During her stormy course she received cyclophosphamide (Cytoxan), vincristine, adriamycin, bleomycin, chlorambucil, vinblastine, and Methyl CCNU. She never received radiation.

From February 1972, she had numerous admissions for hypotension, anemia, radiculopathy, myelosuppression, and a functional platelet defect, considered to be sequelae of lymphoma or chemotherapy.

On April 2, 1974, an eye lesion was first recorded in the hospital chart; however, the patient stated she noticed a red growth in her left eye in early 1972, which appeared stable or slow growing.

Because of diplopia with left laterally directed gaze, ophthalmologic consultation was obtained in May 1974. Subsequent examination was essentially normal except for a large, fleshy, tan mass at the nasal corneoscleral limbus with encroachment of the cornea, which prevented full lateral excursion of the left eye and caused diplopia on left laterally directed gaze. The presumptive diagnosis was lymphomatous infiltrate of the conjunctiva (Fig. 1).

On June 8, the mass was removed, and permanent section disclosed a moderately differentiated squamous cell carcinoma (Figs. 2 and 3).

On July 9, the patient underwent resection of the medial conjunctiva to the caruncle. Frozen section at surgery revealed the margins to be free of tumor, and a mucous membrane graft from the lip was placed over the operative site. Permanent section, two days later, again disclosed tumor in the margins.

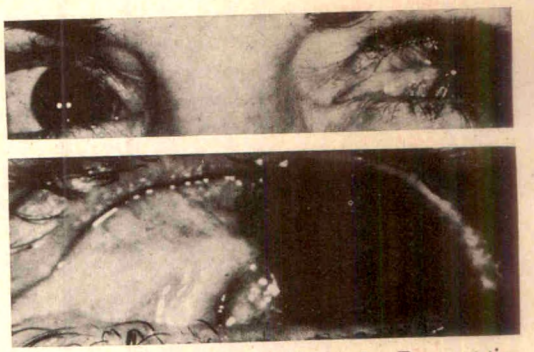


Fig. 1 (Kushner and Mushen). Preoperative pterygoid appearance of conjunctival lesion.

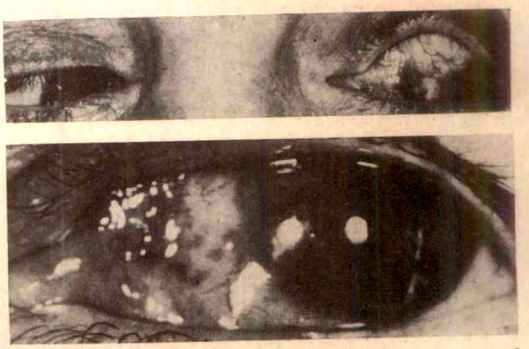


Fig. 2 (Kushner and Mushen). Appearance of lesion after biopsy with lamellar keratectomy.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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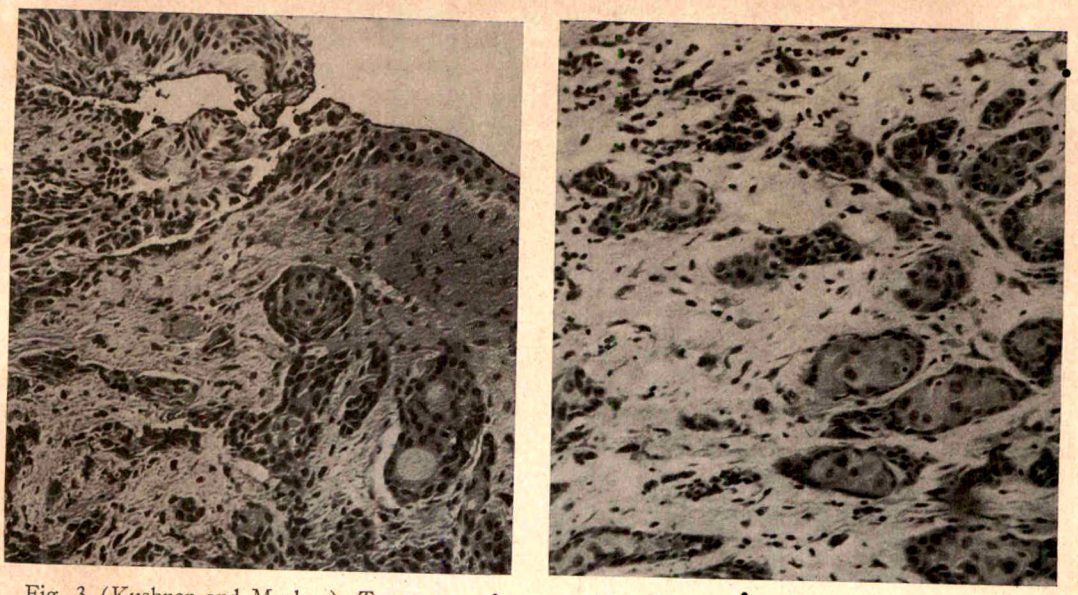


Fig. 3 (Kushner and Mushen). Two areas of permanent section of tumor, moderately differentiated squamous cell carcinoma (hematoxylin and eosin, ×250).

We irradiated the lesion, and the patient received only 3,000 rads of cobalt therapy of a planned dosage of 5,000 interrupted by the occurrence of a spontaneous pneumothorax.

There was recurrence of the tumor at the caruncle; limited lateral excursion and concomitant diplopia were a problem. Intraocular invasion did not occur. Her general condition deteriorated as the lymphoma invaded the bone marrow, and frank leukemic transformation took place.

Discussion

Patients with one primary malignancy are more prone to contract another.[10-13] Lymphoma is perhaps a prime culprit in this circumstance,[12,13] as the host's immune system is commonly altered by this disease.[10] Patients with lymphoma and three or four other primary tumors were reported,[10-12] although, to our knowledge, this is the first report of a squamous cell carcinoma of the conjunctiva as a second primary tumor.

Evidence suggests that tumor-specific antigens exist which identify cells, so the immune system may survey, process, eliminate, or restrict neoplastic cells identified as foreign. If the immunologic system is altered or compromised either by disease or immunosuppressive therapy, these tumor antigens might not be discerned, and patients would have an increased risk of neoplasia.[10]

Tumors have been reported as a supposed consequence of radiation therapy, cancer chemotherapy, and immunosuppressive regimens for transplantation.[10]

Other theories hypothesize that viral infections produce neoplasia, and weakened immune response resulting from drugs or disease may allow proliferation of oncogenic viruses that normally reside quiescently in the host.[10]

Squamous cell carcinoma of the conjunctiva in our patient, which may have arisen de novo or as a result of malignant deterioration of a pterygium, as suggested by Sevel and Sealy,[6] is an atypical epidemiologic example of a rare disease.

Although data regarding incidence and prevalence are scarce, the inference is that epithelioma of the conjunctiva is usually an affliction of men over 50. In industrialized, temperate countries, 75% of the cases occur in men, and over 90% are men over 50 years of age.[2,4,7] In the United States, it comprises from 5 to 9% of all eye cancers,[2] while in Africa, the incidence is almost 17% of the eye tumors.[8] The authors of one Indian study[9] reported only three cases of 35,000 patients visiting their clinic (one of which

was the fourth reported case of bilateral squamous cell carcinoma of the conjunctiva).

Various theories of etiology have been advanced. The fact that the disease is more common among equatorial Africans and men of the southern and southwestern parts of the United States, as well as the penchant of the tumor for the nasal-limbal location, suggests exposure to ultraviolet light as the most important cause,[3,4,6,7] although, chronic local irritation, pre-existing trauma, or local inflammation may play a role in etiology.[6]

However, our patient—with one debilitating primary malignancy, chronically ill, and shut-in—received less than normal exposure to ultraviolet light or the capricious winds, despite her south Texas location.

The fact that she contracted a rare ocular tumor with a predilection for older men who are exposed to the elements raises questions of tumor immunology: (1) What is the relationship between the primary lymphoma with its implicit alteration of the immune system and the ocular cancer? (2) What is the relationship between the several regimens of immunosuppressive chemotherapy and the second primary malignancy? (3) Does the combination of chemotherapy and lymphocytic tumor—two alterations of the immune system—mitigate more favorably toward the appearance of the ocular tumor than either state alone?[7]

A relationship between these factors may be responsible for the occurrence of this rare tumor in this particular epidemiologically low-risk patient.

Findings in this case indicate that oncologists as well as ophthalmologists should be aware of the possible appearance of rare ocular tumors in patients with compromised immune status. Our patient's course suggests that seemingly innocuous lesions, such as pingueculae or pterygia, should be followed closely, biopsies should be done, and the lesions treated definitively in patients who have altered immune states, either from primary diseases of the immune system, chemotherapeutic or radiotherapeutic regimens, or transplantation preparatory immunosuppressive therapy.

Addendum—In December 1974, shortly after the preparation of this paper, the patient died of myelomonocytic leukemia. After her death, we discovered her immune status had been studied in December 1973.

Relevant data at that time were as follows: (1) Response to common mitogens included phytohemagglutin, 24.8 (normal, 88); pokeweed mitogen, 10.6 (normal, 44); Concanavalin A, 21.7 (normal, 63.5). (2) Blastogenic responses to the specific antigens —tetanus, *Monilia*, herpes simplex 1 and 2, and varicella zoster—yielded a blastogenic index of less than 3. Normal responses are greater than 3. (3) Immunoglobulin determinations included IgG, 650 (normal, 800-1,800); IgM, 37 (normal, 70-200); IgA, 99 (normal, 99-450); and IgD, 3.1 (normal, 0.3-40).

These data support the contention that her immune system was severely altered by the primary disease or the chemotherapeutic regimen, or both, and lend additional credence to the hypothesis that the patient was susceptible to incurring a second malignancy.

Summary

A 31-year-old white woman with a poorly differentiated malignant lymphoma and a compromised immune system atypically contracted squamous cell carcinoma. Data obtained after her death indicate that her immune system was severely altered by either the primary disease or the chemotherapeutic regimen, or both.

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OPHTHALMIC MINIATURE

One day coming back to Paris from Nice, I got a cinder in my eye and nothing I did for that eye made it any better. It grew horribly inflamed. Eyelids, upper and lower, were bloated red and the eyeball itself was hideously criss-crossed with scarlet veins. I had conjunctivitis. There was nothing to do but call a French doctor. He prescribed blue eyedrops. I'd never seen anything like them before and I knew they'd blind me. But the conjunctivitis was going to do that anyway, and to hurry up my inescapable fate and get it over with, I used the eyedrops. When the blue of those drops met the red of my eyes, the effect was dramatic. By dyeing the whole eyeball blue they gave me the illusion for a good ten minutes that I'd been instantaneously cured of the disease. And they were soothing. They were wonderful. In the end they did cure the conjunctivitis, and even now whenever my eyes are inflamed I use them with perfect confidence. Next time you see me in a colour film and remark the fresh tint of the whites of my eyes, it's not the good clean life I lead, it's my French blue eye drops.

Olivia de Havilland,
Every Frenchman Has One

CORRECTION OF DISTICHIASIS BY TARSAL RESECTION AND MUCOUS MEMBRANE GRAFTING

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Distichiasis is a rare congenital abnormality in which an accessory row of eyelashes lies posteriorly to the normal lashes.

To correct the disorder Fox[1] split the lower eyelid along the gray line to divide it into anterior and posterior parts. A vertical incision through the tarsoconjunctival lamina near each canthus created a sliding flap. The upper 3 mm of this flap, including the accessory cilia, were resected. The cut edge was pulled up to slightly above the edge of the anterior skin muscle lamina and sutured in place.

Nicati[2] corrected distichiasis by splitting the eyelid at the gray line and resecting the tarsoconjunctival strip bearing the accessory cilia.

Begle[3] improved this method by covering the bared area with a buccal mucous membrane graft. Otherwise treatment has consisted of repeated epilation[4] or electrolysis.[5]

CASE REPORT

An 8-year-old boy had surgical correction on his right upper eyelid in February 1973, and on his left upper eyelid in June 1974 (Figs. 1 and 2). The patient had distichiasis of all four eyelids. The accessory lashes were more numerous in the upper eyelids than in the lower eyelids. The accessory cilia in the lower eyelids were removed by electrolysis. The distichiasis of the upper eyelids was corrected by using an operating microscope.

The upper eyelid was everted over an eyelid plate and held in position by two traction sutures. An incision was made through the conjunctiva into the tarsus 1 mm within and parallel to the eyelid margin. This incision was carried medially and laterally to beyond the limits of the accessory lashes. The incision was deepened until all the lashes had been cut across. This was easily seen through the operating microscope. The incision was carried slightly deeper to approximately two thirds the depth of the tarsus. A parallel incision was made 3 mm from the first and made equal in length and depth. The two incisions were joined medially and laterally. The incisions corresponded to the dotted line seen in Figure 3. The tarsus within the incision line was dissected off. This part of the tarsus contained the roots of the lashes (Fig. 4). A buccal mucous membrane graft was tailored to fit the defect in the tarsus and sutured

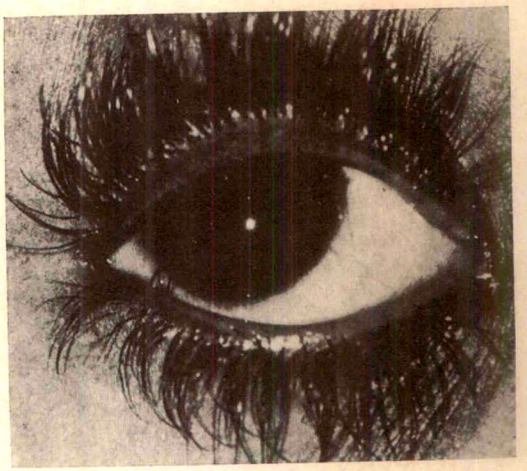


Fig. 1 (White). Preoperative appearance of right upper eyelid.

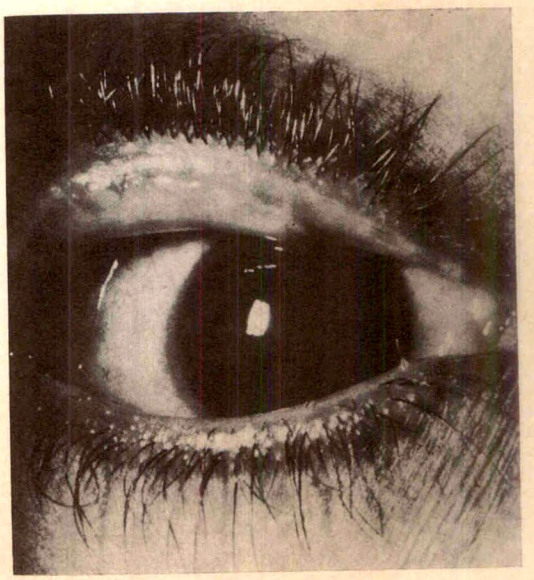


Fig. 2 (White). Right upper eyelid elevated to show postoperative appearance of internal surface.

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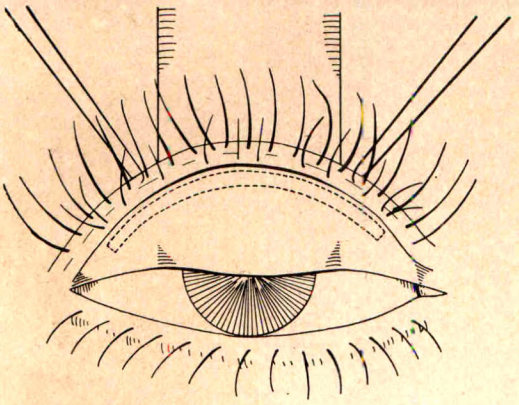


Fig. 3 (White). Incision lines on internal eyelid surface.

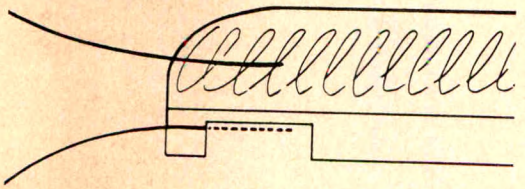


Fig. 4 (White). Cross section of upper eyelid.

in place by using a continuous 6/0 plain catgut suture. The eyelid plate and traction sutures were removed and the eyelids closed after the application of antibiotic ointment. A firm pressure dressing was applied, changed daily, and maintained for five days postoperatively.

Discussion

Previous surgical techniques for the correction of distichiasis are not wholly satisfactory.

Continued epilation has obvious disadvantages. Electrolysis is suitable only when a limited number of accessory cilia are present. Correction by advancement of the posterior lamina would appear to be confined to distichiasis of the lower eyelids. Such a technique applied to the upper eyelid might be expected to elevate the eyelid. Fox[1] did not describe its use in the upper eyelid.

Resection of the cilia-bearing margin, with or without mucosal grafting, not only may lead to entropion but it produces a rounded, nonphysiological posterior eyelid margin unattractive in appearance.

The technique described preserves the essential posterior eyelid margin and retains its tear flow properties. The retention of one third of the tarsal thickness maintains its flat formation and the anterior lower surface of the tarsus, into which part of the levator muscle is inserted, is undisturbed. Retention of this insertion may play an important role in the prevention of entropion. No entropion has yet been seen in either eyelid operated on by using this technique. No lash with an excised root has regenerated. This method, using the advantages of modern instrumentation, offers some practical as well as theoretical improvement.

Summary

Using the operating microscope in a surgical technique for the correction of distichiasis, the partial thickness strip of tarsus lying within the eyelid margin, which contains the roots of the lashes, was excised and replaced by a buccal mucous membrane graft.

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BACTERIAL ENDOPHTHALMITIS FOLLOWING SUTURE REMOVAL AFTER PENETRATING KERATOPLASTY

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Endophthalmitis has been documented after cataract extraction,[1] filtering procedures,[2] and retinal detachment repair.[3] However, endophthalmitis has not been reported to be a complication following suture removal after keratoplasty. We present three cases of proven bacterial endophthalmitis following suture removal after penetrating keratoplasty: two are associated with wound dehiscence and one without dehiscence.

METHOD

Suture removal after keratoplasty was performed at a slit-lamp biomicroscope or under an operating microscope. Sterile suture removal sets consisting of a wire eyelid speculum, razor blade, blade breaker, and fine jeweler's forceps were used in conjunction with topical proparacaine hydrochloride.

CASE REPORTS

Case 1—A 59-year-old white woman was seen in the outpatient department with bilateral Fuchs' endothelial corneal dystrophy, severe endothelial guttate changes, and lenticular nuclear sclerosis. A trial with bandage soft contact lenses and hypertonic saline failed to improve visual acuity.

On Oct. 5, 1971, when her best corrected visual acuity was R.E.: 20/200, and L.E.: 20/60, we performed an 8.0-mm penetrating keratoplasty using a continuous 10-0 monofilament nylon suture, an intracapsular cataract extraction, and two peripheral iridotomies in the right eye. At the completion of surgery, 40 mg of gentamicin was injected subconjunctivally.

Her postoperative course was characterized by a graft that remained clear and thin, with normal intraocular pressure. Early postoperative therapy included topically applied atropine 1%, dexamethasone (Decadron) 0.1%, polymyxin B sulfate (Neosporin), and orally administered acetazolamide. These were discontinued or tapered so that after 12 weeks, she received only dexamethasone and polymyxin B sulfate, once daily. Seven months postoperatively, when best visual acuity was R.E.: 20/60, the continuous nylon suture was removed uneventfully. Topically applied polymyxin B sulfate and dexamethasone were continued once daily. The next morning the graft was intact.

Four days after suture removal she was admitted because of a one-day history of pain, photophobia, and visual acuity decreased to light perception with fair projection. There was a thickened, edematous graft with an anterior wound dehiscence in one quadrant, and a severe fibrinous iritis, without hypopyon. The wound was cultured immediately, and she was treated intensively with antibiotics and corticosteroids. Within 24 hours, the cornea became more opaque and the culture revealed *Diplococcus pneumoniae*. Intensive medical as well as surgical therapy failed to save the eye, as she ultimately lost light perception and developed phthisis bulbi.

Case 2—A 68-year-old white woman, bilaterally aphakic, was followed in the outpatient department for medically controlled glaucoma. Visual acuity was R.E.: light perception, due to glaucomatous optic atrophy, and L.E.: 20/60 initially, that slowly deteriorated to 20/200 due to bullous keratopathy, despite therapy with a bandage soft contact lens and hypertonic saline.

On Feb. 15, 1972, we performed a 7.5-mm penetrating keratoplasty in her left eye, using a continuous 10-0 nylon monofilament suture, two peripheral iridotomies, and an anterior vitrectomy. After surgery, we injected 20 mg of gentamicin and 30 mg of methylprednisolone acetate (Depo-Medrol) in the inferior cul-de-sac. Postoperatively she had a transient secondary glaucoma that required no medication after four weeks. Topical chloramphenicol (Chloromycetin) and dexamethasone were used in decreasing dose regimens. At the time of suture removal only 0.005% dexamethasone was being used, once daily.

On Aug. 21, 1972, six months postoperatively, the continuous nylon suture was removed. Immediately after removal we noted a slight temporal anterior wound separation; however, there was no evidence of posterior dehiscence or wound leak. She was treated with a soft contact lens in an attempt to correct the anterior wound dehiscence, and the chloramphenicol drops were restarted, three times daily.

Two days later the patient complained of pain in her left eye that had begun the previous evening. Her eye had severe conjunctival injection, with moderate mucous discharge, a hazy cornea

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with a 270-degree full-thickness separation, and a shallow anterior chamber with a hypopyon. Visual acuity was hand motions. An anterior chamber paracentesis was performed for culture and Gram stain; the latter showed no organisms. Immediate intensive antibiotic therapy was instituted after wound repair with 7-0 black silk sutures. In 24 hours the culture grew *Proteus mirabilis*, while the infection appeared worse. Despite medical and surgical therapy, best visual acuity was counting fingers due to graft failure.

Case 3—A 28-year-old white woman had sustained a chromic acid burn of her right eye in 1966, and had undergone successive lamellar and penetrating keratoplasties that failed. Subsequently she was fitted with a flush-fitting scleral shell and was treated with topical methylcellulose for the chemically induced dry eye. Visual acuity prior to a second penetrating keratoplasty was light perception.

On Sept. 11, 1973, we performed a resection of subconjunctival pannus, intracapsular cataract extraction, anterior vitrectomy, and a 7.0-mm penetrating keratoplasty using interrupted 10-0 monofilament nylon sutures. Twenty milligrams of gentamicin and 20 mg of methylprednisolone acetate were injected subconjunctivally at the end of surgery. The next day two sutures that were loose temporally were replaced in the operating room with 10-0 nylon sutures; 20 mg of gentamicin was again injected subconjunctivally after placement of the additional sutures.

Postoperatively the graft remained clear and thin, and the intraocular pressure was normal. She was treated with 60 mg of oral prednisone, daily, tapered to 40 mg at the time of hospital discharge; 50 mg of methazolamide (Neptazane), three times daily, until discharge; and chloramphenicol 0.25% and dexamethasone 0.1%, each four times daily. A soft contact lens promoted epithelialization of the graft.

Four weeks postoperatively her visual acuity was R.E.: 20/400, the cornea was clear, and the ocular tension was normal. The soft contact lens was discontinued. Two nasal sutures were removed because of vascularization around them without complication. We tapered the prednisone therapy to 15 mg daily, continued dexamethasone 0.1%, once daily, and discontinued chloramphenicol.

Five days later the patient presented with a two-day history of pain, redness, and decreased vision. Her acuity was light perception. There was some superficial thinning of the graft between 10 and 1 o'clock superiorly, a hypopyon was present, and there was no evidence of wound separation. We diagnosed endophthalmitis, and performed an anterior chamber paracentesis. Although the Gram stain of the aspirate failed to reveal any organisms, she was treated intensively with antibiotics. The culture of the paracentesis aspirate eventually grew *Staphylococcus aureus* but despite intensive medical therapy, the infection worsened. Visual acuity was barely light perception in her right eye and on last examination she appeared to be developing phthisis bulbi.

Discussion

The recent improvement in the prognosis for successful keratoplasty is probably based on two factors: instrumentation and corticosteroids. The operating microscope with its high resolution and the use of finer suture material have permitted more accurate alignment of the corneal endothelium. Fine sutures appear to stimulate less vascular growth and less tissue reaction. More accurate donor-host alignment of the graft and less graft neovascularization have probably reduced the incidence of surgical failures and graft reactions.[4] The MacKay-Marg tonometer, which assists in the early recognition of increased intraocular pressure after keratoplasty,[5] and the pachymeter, which permits detection of subtle changes in corneal thickness reflecting hydration, are two other instruments that have improved the keratoplasty prognosis. More recently, the vitreous suction cutter has been used to aid the surgeon in dealing with the vitreous in aphakic keratoplasty.[6,7] In addition, the use of the bandage soft contact lens has clearly played a significant role in preserving donor epithelium in those eyes with poor healing tendencies, such as those with chemical injury.[8] Proper timing of suture removal and prompt diagnosis and institution of corticosteroid therapy for graft reactions appear also to improve the results in these poor prognosis cases.[9]

The use of extra fine suture material that stimulates less corneal vascularization may be a double-edged sword, because it may produce delayed corneal wound healing and predispose to wound dehiscence on suture removal.[4,10] Wound dehiscence may be the single most important factor providing a portal of entry for bacteria into the eye after keratoplasty. Open suture tracts, or vitreous strands incarcerated in the wound, may also be contributing factors.

The first two patients developed endophthalmitis seven and six months, respectively,

after keratoplasty when the continuous 10-0 monofilament nylon suture was removed. In each of these cases, wound dehiscence preceded the development of endophthalmitis. Each of these patients had been maintained on topical corticosteroids after keratoplasty, a factor that may have contributed to the propensity for infection. Topical corticosteroids may also contribute to delayed wound healing, although most experimental evidence only shows delayed healing in the early postoperative period.[11-13] The third patient with a chemical corneal injury was placed on systemic as well as topical corticosteroids after keratoplasty. In addition, we performed suture removal in this case relatively early in the postoperative period, but this is common for a severely vascularized cornea.

With regard to antibiotic therapy, none of the patients were treated with systemic antibiotics after keratoplasty, but all were receiving topical antibiotics postoperatively, possibly altering the bacterial flora. Immediately after suture removal, one patient (Case 3) received no topical antibiotics while another patient (Case 1) was treated with polymyxin B sulfate, one drop daily, and another (Case 2) was treated with chloramphenicol, three drops daily.

The use of soft contact lenses to aid in corneal re-epithelization[8] and to help support corneal wounds has been advocated.[14,15] At our institution these lenses are thermally sterilized prior to use and are usually used in conjunction with freshly prepared sterile 0.25% chloramphenicol ophthalmic solution without preservatives. Because of these precautions, it is unlikely that the soft contact lens was the source of infection in Case 2. We removed the soft contact in one patient (Case 3) prior to suture removal and it is possible that the absence of the lens may have permitted organisms to enter the suture tracts. Organisms also may have been introduced into the conjunctival sac at the time of lens removal.

The prognosis for visual recovery in cases of endophthalmitis is routinely poor, even with early diagnosis and treatment. Approximately two thirds of patients recover no useful vision and this figure has not appreciably changed in the era of antibiotics.[16] Because of this grim outlook, prevention and suspicion appear to be the best measures. Suture removal without evidence of wound separation rarely leads to late bacterial endophthalmitis (Case 3 was one case in over 900 keratoplasties from Jan. 1, 1971, to June 1974); however, this report should alert corneal and cataract surgeons that such a sequela can occur.

Evaluating wound integrity and judging the optimal time for suture removal are often extremely difficult. Deep vascularization, wound contraction, suture loosening, and appearance of the wound scar are helpful clues but there is little objective evidence about the "wound glue," and one must usually rely on clinical judgment. The suture removal technique is important and strict asepsis should be maintained. Careful observations should be made for anterior wound separation, full-thickness dehiscence, and anterior chamber shallowing. Wound integrity itself may be aided in the immediate 24-hour postsuture removal period by using a pressure patch, and the surgeon should definitely evaluate the wound the following day. If there is a clinical wound separation, appropriate measures for correction should be undertaken. In addition it also seems reasonable to attempt to decrease the bacterial flora with topical antibiotics, administered immediately prior to suture removal and for several days afterward. However, even the use of topical antibiotics and a careful follow-up may not prevent endophthalmitis, as demonstrated here: two patients received topical antibiotics and two patients developed symptoms as late as the third day after suture removal. Because of the possibility of late wound separation, one should alert the patient to the signs and symptoms of wound dehiscence and infection so that the patient will return quickly for examination, diagnosis, and immediate institution of therapy.

Summary

Of three cases of bacterial endophthalmitis occurring after removal of corneal sutures following penetrating keratoplasty, two were associated with wound dehiscence and one was not. Factors that may predispose to wound dehiscence and subsequent infection are: use of fine suture material, corticosteroids, and chronic topical antibiotics; early removal of corneal sutures; lack of adherence to strict asepsis prior to and after suture removal; and open suture tracts that may be kept open by incarceration of vitreous strands.

Late corneal wound dehiscence may occur with subsequent development of endophthalmitis as long as three days after suture removal. The use of topical antibiotics before and after suture removal may decrease the potential for infection. In addition, early recognition of intraocular infection by the patient and the surgeon for immediate institution of antimicrobial and anti-inflammatory therapy may preserve useful vision.

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THE EFFECT OF CORTICOSTEROIDS IN THE TREATMENT OF EXPERIMENTAL BACTERIAL ENDOPHTHALMITIS

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The role of corticosteroids in the treatment of bacterial endophthalmitis is still controversial. The problems in assessing the value of corticosteroids arise from variations in the severity of the initial disease, the promptness with which it is recognized, and the adequacy of antimicrobial therapy in terms of drug, dose, and route. The use of an experimental model helps to control many of the variables.

Few investigators have examined the effects of corticosteroid therapy on the outcome of experimental bacterial endophthalmitis. Maylath and Leopold[1] demonstrated that the addition of subconjunctival cortisone to therapy with penicillin G or chloramphenicol improved the results of therapy in staphylococcal endophthalmitis in rabbits. This was true, however, only when the corticosteroid was given within four hours of the initiation of infection; a delay of 12 hours yielded a poor outcome regardless of therapy. Moreover, the results were only assessed four days after the onset of therapy.

Peters and associates[2] demonstrated the mobilization of leukocytes from blood to a skin chamber to be slightly inhibited by prednisone and increased by dexamethasone. They suggested that the difference in the effect of the two corticosteroids might be relevant in situations where granulocyte migration was important in defending against bacterial invasion during corticosteroid therapy.

We examined the effects of retrobulbar administration of dexamethasone or prednisolone, together with pencillin G, on the outcome of staphylococcal endophthalmitis in rabbits.

MATERIALS AND METHODS

We used albino rabbits, 1.5 to 2.0 kg, of either sex. An endophthalmitis was produced in both eyes of each rabbit (day 0) by injecting 0.1 ml of a 10^{-7} dilution of an overnight growth of a penicillin G-sensitive strain of *Staphylococcus aureus* into the vitreous cavity through the pars plana. The inoculum was standardized by using a Gilford photometer and contained approximately six colony-forming units. Treatment was initiated 24 hours after infection (day 1) and was administered each day for ten consecutive days. The following treatment groups were studied: in Group A, 50 eyes received 100 mg of penicillin G (0.32 ml); in Group B, 74 eyes received 100 mg of penicillin G (0.32 ml), and 25 mg of prednisolone sodium succinate (Meticortelone soluble) (1 ml); in Group C, 74 eyes received 100 mg of penicillin G (0.32 ml), and 4 mg of dexamethasone sodium phosphate (Decadron phosphate) (1 ml); and in Group D, 20 eyes received a normal saline control (1 ml).

In addition, four animals with normal eyes were treated; two received penicillin and dexamethasone and two received penicillin and prednisolone as above.

Retrobulbar injections were performed through the conjunctiva with a 1-ml disposable tuberculin syringe and a 25-gauge 5/8-inch needle. Each drug was injected separately. The left and right eyes of each animal

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received the same treatment. In Group A, a retrobulbar injection of 1 ml of saline was given in place of the corticosteroid.

All eyes were normal before the experiment. Each was examined daily for the first ten days as well as on days 30 and 60. Animals dying before day 5 were not included in the study results. The experiment was terminated at day 60. All eyes were dilated for the first ten days with 1% atropine eyedrops and the atropine was maintained until the eyes whitened. Examination consisted of penlight and slit-lamp observation, and direct ophthalmoscopy. Changes in eyelids and all ocular tissues were recorded. We used the following grades to evaluate changes in the vitreous cavities and retinas: 0, normal vitreous and retina or a few cells in the vitreous; 1, excellent red reflex with hazy fundus details; 2, good red reflex and fundus not visible; 3, poor red reflex; and 4, no red reflex.

All animals were weighed periodically throughout the experiment. At the conclusion of the experiment eyes with opaque media were sectioned horizontally and examined with a dissecting microscope. We examined multiple histopathologic sections, stained with hemotoxylin and eosin.

Statistical analysis of the data was performed by χ^2 tests of independence.

Results

Initially, there were 113 rabbits but by day 60, only 59 animals were alive. Most died during three summer months when epidemic diarrhea of unexplained etiology was prevalent in the animal quarters. The death rates for the various treatment groups during the epidemic diarrhea were Group A (penicillin G), 6 of 10 (60%); Groups B and C (penicillin G and corticosteroid), 28 of 38 (74%); and Group D (saline control), 2 of 4 (50%). Fifteen other animals died during the experiment, some with diarrhea, others for no apparent cause. In addition, 21 eyes were excluded from the analysis for reasons other than death. Corneal ulcers developed in 14 eyes precluding visualization of the posterior segment; all occurred in the corticosteroid-treated groups. The other seven eyes were eliminated because they never exhibited signs of infection; five of these occurred in the groups receiving corticosteroids, one in the group receiving penicillin G alone, and one in the saline control group.

Figure 1 depicts the distribution of ophthalmoscopic findings during the first four days. To simplify the analysis, we pooled data for the two corticosteroid-treated groups, and combined the injuries of grades 2 to 4. During the first 24 hours after infection, most eyes in each group exhibited only trivial abnormalities. By 48 hours, however, severe changes were evident in all groups and persisted through day 4. Chi-square tests of independence showed no significant differences in lesion distribution among these three groups at day 1. In contrast, animals receiving penicillin G exhibited significantly more severe injuries than those receiving pencillin G and a corticosteroid on day 2 ($P = .005$), day 3 ($P = .025$), and day 4 ($P = .05$). Neither group differed significantly from the saline-treated animals during days 1 to 4.

By day 10, eyes comprised grades 0, 1, and 2 in the following manner: penicillin G and corticosteroids—19, 32, and 41%; penicillin G—8, 32, and 60%; and saline—7, 7, and 86%. While the penicillin G and corticosteroid-treated group did not differ significantly from the penicillin G-treated animals, both exhibited better results than the saline controls ($P < .05$).

On day 60 (Fig. 2), we noted a significant difference between eyes treated with penicillin G and corticosteroids and those receiving only penicillin G. The fundi were not visible in 61.1% of eyes treated with antibiotic alone, in contrast to 35.8% of eyes receiving corticosteroids ($P < .025$). There was no significant difference when the results of the group receiving prednisolone were compared with the dexamethasone results. Thus,

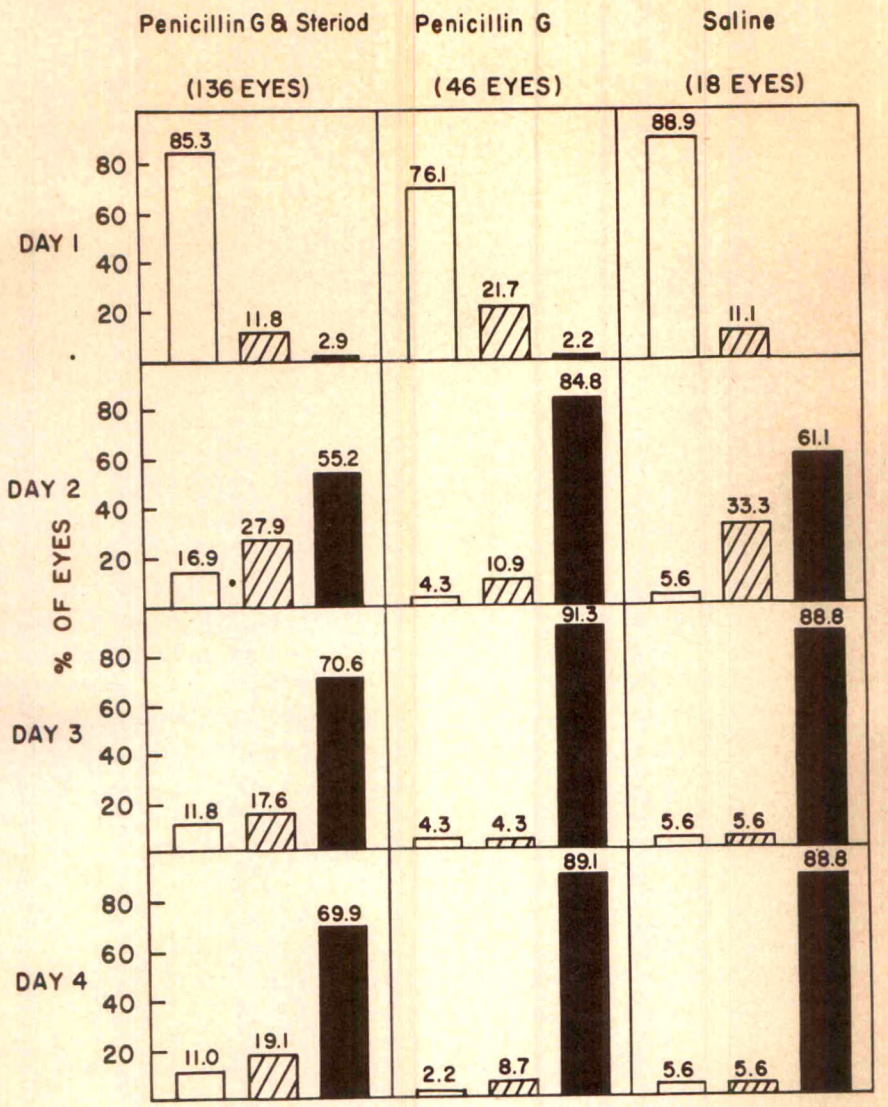


Fig. 1 (Baum and associates). Response of eyes on days 1 to 4. Clear bars indicate grade 0; striped bars, grade 1; and black bars, grades 2 to 4. See text for explanation of grading.

62% of eyes treated with penicillin G and prednisolone, and 65% of eyes treated with penicillin G and dexamethasone had grades 0 or 1 injuries. The four animals with normal eyes who received antibiotics and corticosteroids exhibited no signs of ocular inflammation.

Ophthalmoscopic examination performed at day 60 on eyes in grades 0 and 1 revealed small white retinal patches in most eyes. These patches were usually smaller than 1 disk diameter and one to four patches were typically seen in each eye. Large, white patches rarely occupied as much as a quadrant of the retina. However, most of the retina in eyes in grades 0 and 1 appeared grossly normal. Eyes with opaque media, when opened and examined with a dissecting microscope, invariably revealed organized vitreous humor.

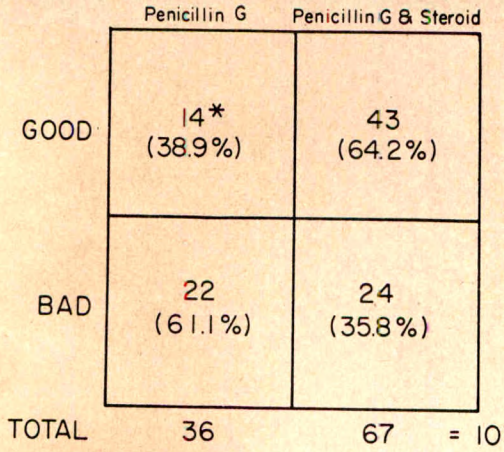


Fig. 2 (Baum and associates). Comparison of results of treatment with penicillin G or penicillin G and corticosteroids at day 60. Good indicates grades 0 and 1; bad, grades 2 to 4; asterisk, eyes.

Histopathologic examination of diseased eyes in grades 2 to 4 examined after day 60 revealed marked diffuse retinal destruction. Eyes in grades 0 and 1 had infrequent small areas of atrophic retina. These atrophic areas probably correspond to the white retinal patches seen ophthalmoscopically at day 60.

Discussion

The results indicate the retrobulbar administration of corticosteroids exerts a beneficial effect on the outcome of experimental bacterial endophthalmitis when used in combination with effective antibiotic therapy.

Our grading on the severity of the ocular lesions is admittedly arbitrary, but a counterpart exists in human disease. The degree of resolution of bacterial endophthalmitis in man is measured in terms of vitreous opacities, retinal damage, and loss of vision. While we could not evaluate the last criterion, the first two were easily assessed. Because prolonged observation may be necessary to establish the extent of residual damage, final grading was performed after 60 days. This interval is presumably sufficient to distinguish temporary infiltrative lesions from permanent tissue destruction, cicatrization, and organization.

Therapy was instituted 24 hours after the initiation of infection at a time when most eyes were still clinically normal. By day 2, we categorized more than 80% of the eyes in each group in grades 1 to 4. This persisted through day 10. The extent of damage did not differ among the treated groups on day 10. By day 60, however, there was a significant difference among animals receiving various forms of therapy.

Penicillin G alone produced good results —grades 0 and 1—in approximately 40% of eyes, while the addition of corticosteroids increased this proportion to 64%. The difference was significant by a χ^2 test ($P < .025$).

Only 59 of 103 rabbits remained in the experiment on day 60. Deaths during the experiment were equally distributed among the different treatment and control groups. Development of corneal ulcers eliminated 14 additional eyes from the study. Only eyes receiving corticosteroid therapy developed such ulcers, possibly because corticosteroids increase the susceptibility of the cornea to infection.

Peters and associates[2] suggested that the difference in mobilizing polymorphonuclear leukocytes between prednisone and dexamethasone may be relevant when extravascular granulocytes are important in defense against bacterial invasion. The response to these two corticosteroids was almost identical in our study.

Summary

We evaluated the effects of the addition of corticosteroids to antibiotic therapy in the treatment of staphylococcal endophthalmitis in rabbits. Twenty-four hours after the induction of infection with *Staphylococcus aureus,* penicillin G, penicillin G and dexamethasone or prednisolone, or saline was injected retrobulbarly for ten days. Afterward, there was no ophthalmoscopic difference between the penicillin and cortico-

steroid-treated group and those animals receiving only penicillin G. At day 60, however, the fundus was visible in 64% of eyes treated with penicillin G with corticosteroids in contrast to 39% of those eyes treated only with penicillin G ($P < .025$). The results between dexamethasone and prednisolone use were not significant. Retrobulbar corticosteroids in combination with effective antibiotic therapy effectively treated experimental bacterial endophthalmitis.

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Ophthalmic miniature

And thus ends all that I doubt I shall ever be able to do with my own eyes in the keeping of my Journal, I being not able to do it any longer, having done now so long as to undo my eyes almost every time that I take a pen in my hand; and, therefore, whatever comes of it, I must forbear: and, therefore, resolve, from this time forward, to have it kept by my people in long-hand, and must therefore be contented to set down no more than is fit for them and all the world to know; or, if there be anything, which cannot be much, now my amours to Deb. are past, and my eyes hindering me in almost all other pleasures, I must endeavour to keep a margin in my book open, to add here and there, a note in short-hand with my own hand.

And so I betake myself to that course, which is almost as much as to see myself go into my grave: for which, and all the discomforts that will accompany my being blind, the good God prepare me!

Diary of Samuel Pepys
May 31, 1669

THE ROLE OF CYTOLYSIN IN PNEUMOCOCCAL OCULAR INFECTION

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The mechanism of pathogenicity has not yet been established in microbial infections which result in destruction of ocular tissue. Allen[1] suggested the involvement of a toxin and demonstrated that preparations of staphylococcal toxin produced symptoms of conjunctivitis when instilled into the eye. Cross and Nakamura[2] implicated endotoxin in the case of *Escherichia* and *Shigella* infections, and Marzulli, Evans, and Yoder[3] implicated it in keratitis caused by *Pseudomonas aeruginosa*. Other investigators proposed that bacterial enzymes play a role in the pathogenesis of corneal infections. Proteases were implicated in the case of *P. aeruginosa* by Fisher and Allen[4,5] and by Kreeger and Griffin,[6] in *Cephalosporium* by Burda and Fisher,[7] and in *Moraxella* by van Bijsterveld.[8]

In a previous report, we[9] described some of the properties of an agent present in pneumococcal extracts which produced corneal damage upon intracorneal injection. We demonstrate that the same pathologic findings are produced by injection of highly purified pneumococcal cytolysin.

MATERIAL AND METHODS

The growth of cells and preparation of cell extracts has been described.[10] We used the initial steps in purification of the cytolysin as described previously, omitting the step involving acid preparation since occasionally considerable loss of activity occurred during this procedure. Ammonium sulfate precipitation was followed by DEAE-cellulose chromatography and gel filtration on Sephadex G-100. Active fractions from the G-100 column were concentrated (in dialysis tubing under vacuum) after addition of sufficient bovine serum albumin to yield a final concentration of 0.1%. The final stages of concentration (from about 10 to 15 ml to 1 to 3 ml) were perfomed in collodion bags which effected concomitant dialysis against phosphate buffer-saline (0.067M potassium phosphate buffer, pH 7.0, with 0.077M sodium chloride). When the cytolysin was further chromatographed, we applied approximately 35 ml of G-100 eluate (which was not concentrated) to a 20- × 2.5-cm column of hydroxylapatite (Bio-Gel HT, modified calcium phosphate) equilibrated with 0.001M sodium phosphate buffer, pH 6.8. Elution of 2.5-ml fractions was effected with a 0.01 to 0.2M linear gradient of sodium phosphate, pH 6.8. The lytic fractions were combined and concentrated. We added 2-mercaptoethanol (0.03M) to all dilute lysin preparations that were partially purified if they were to be stored without freezing, even overnight. Material used for protein determination or disk gel electrophoresis was concentrated to measurable levels without adding bovine serum albumin. We determined the protein content by the method of Lowry.[11] We performed disk gel electrophoresis by the method of Davis,[12] using 7% polyacrylamide and 0.05M Tris-glycine buffer at pH 8.3. The gels were stained with coomassie blue.

The procedure for determination of lytic titer on rabbit erythrocytes was described.[10] The relative hemolytic activity of fractions eluted from the hydroxylapatite column was estimated less precisely by the time required for complete lysis when a 0.02 ml-sample of the fraction was added to 1 ml of red cell suspension, expressed in arbitrary rela-

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tive units. The activity in the area of the peak was more precisely determined by assay of 0.05 ml of 1:100 dilutions for titer determination.

The animals used in these experiments were mature albino rabbits. Intracorneal injection was performed with a 30-gauge needle on rabbits anesthetized with pentobarbital (Nembutal). Solutions used for injection were sterilized with a 0.45-μ filter. The results were typical of those obtained in experiments replicated at least three times.

Results

Cytolysin purified by ammonium sulfate precipitation, DEAE-cellulose chromatography, and gel filtration on Sephadex G-100 was concentrated tenfold. This preparation showed a single protein band when 0.125 ml was tested by acrylamide disk gel electrophoresis. Approximately 0.05 ml of concentrate (containing 3 to 10 μg of protein and 1,000 to 2,500 hemolytic units) was injected intracorneally. The control eye was injected with phosphate-buffered saline containing 0.1% bovine serum albumin. The injection of cytolysin resulted in the appearance of mucopurulent discharge, redness of the conjunctiva, and swelling of the conjunctiva and eyelid within three hours.

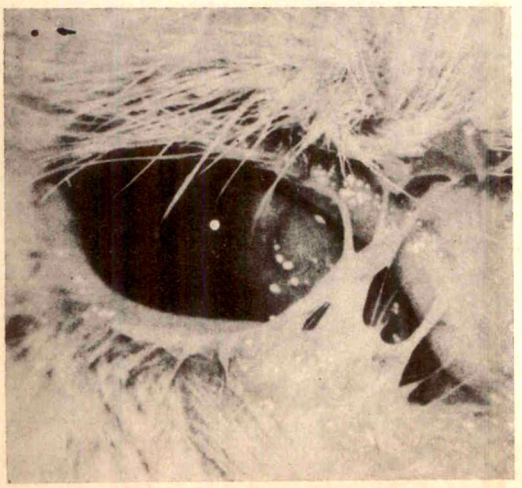


Fig. 1 (Johnson and Allen). Rabbit eye, 24 hours after intracorneal injection of pneumococcal cytolysin.



Fig. 2 (Johnson and Allen). Rabbit eyes, five days after intracorneal injection of pneumococcal cytolysin.

A diffuse corneal haze also resulted, most dense at the site of injection and progressing to complete opacification in 24 hours or less (Fig. 1). Corneal edema and circumcorneal injection were also noted at three hours and increased over the next 24 hours. There was extreme bulging of the cornea two to five days after injection (Fig. 2), reflecting the progressive course of stromal destruction. Complete resolution of the corneal opacification was not noted (one rabbit was observed for 30 days after injection). The control eye showed only a slight and transient corneal haze after injection.

Previously we had noted a difference in the heat sensitivity of cytolysin and of toxin (tested by conjunctival instillation) which led us to believe their identity unlikely.[9] However, the hemolysin was more heat stable in the crude extract (measurable activity persisting even after three minutes at 80°C) than in the partially purified form on which the previous stability measurements were made.

To eliminate the possibility that polysaccharides shed by the Sephadex were responsible for the observed reaction, an equal number of fractions were collected after the elution of the cytolysin and concentrated in the same manner. Intracorneal injection of this material produced no damage.

The purified cytolysin was also tested by conjunctival instillation, since administration of crude pneumococcal extract in this fashion provoked a marked inflammatory reaction with mucopurulent discharge, and reddening and swelling of the conjunctiva.

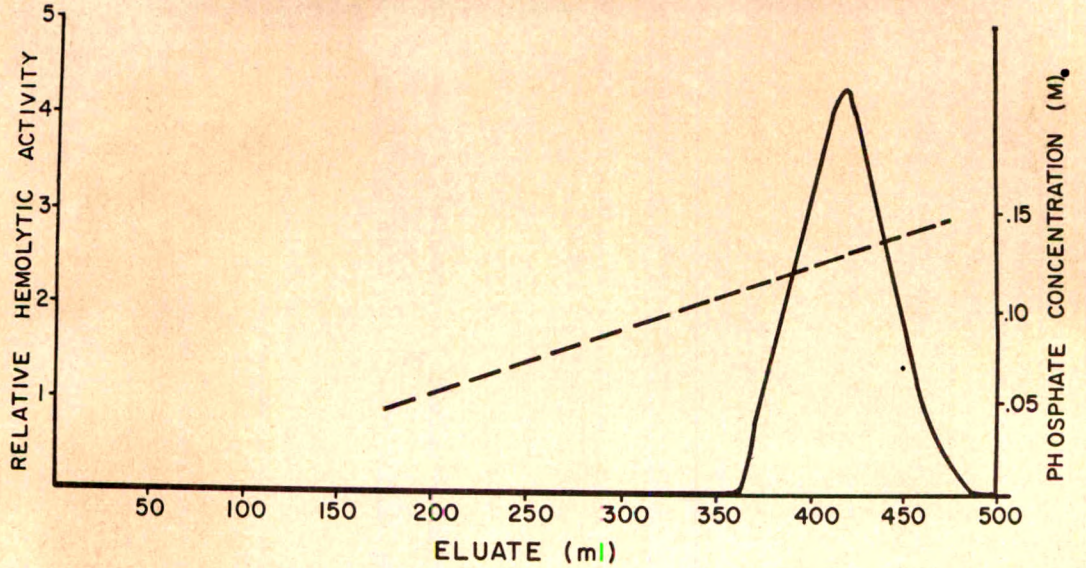


Fig. 3 (Johnson and Allen). Elution of cytolysin from hydroxylapatite column. Broken line indicates phosphate concentration; solid line, hemolytic activity.

Instillation of the purified cytolysin also provoked this response, but not as intensely as the crude extract.

Intracorneal injection of purified cytolysin was responsible for the previously described reaction[9] of the animal to intracorneal injection of crude cell extract. This relationship was confirmed by rechromatography of the G-100 eluate on hydroxylapatite. A single peak of lytic activity was observed (Fig. 3). Protein content of the fractions was too low to monitor spectrophotometrically. When the lytic fractions were combined and concentrated, intracorneal injection of approximately 0.05 to 0.1 ml (containing 3 to 5 μg protein and 1,500 units of hemolysin) produced inflammation, corneal opacification, and bulging. The injection of preparations with increased hemolytic titer produced a more intense reaction. The concentrated lysin showed a single band on disk gel electrophoresis. Therefore, the injury produced by crude pneumococcal extract was caused by pneumococcal cytolysin.

Discussion

In some cases, the tissue damage resulting from ocular infection may arise not from direct action of bacterial enzymes but indirectly, by way of an activation or release of host degradative enzymes (such as collagenase, protease, and mucopolysaccharase) induced by bacterial cytolysins. Bernheimer's[13] review provided evidence that bacterial lysins can lyse or damage many types of mammalian cells and subcellular elements. Itoi and associates[14] and Brown, Akiya, and Weller[15] showed that corneal collagenase is activated as a result of trauma or ulceration. The enzyme originates from both epithelial cells and from stromal fibroblasts and polymorphonuclear leukocytes.[16] Slansky and Dohlman[17] suggested "it may be that any epithelial pathological condition, be it viral, bacterial, traumatic, or chemical in origin, may influence the production or release of this (meaning collagenase) and other degradative enzymes, with stromal destruction the final common pathway." Our results suggest a mechanism (that is, cytolytic action) by which this sequence may be initiated during infection. We plan to demonstrate such a mechanism directly by testing corneal explants for the release of degradative enzymes after lysin injection.

The difficulties involved in quantitation

of the reactions observed in the rabbit after toxic material administration make it impossible to state that the total reaction produced upon instillation or intracorneal injection of crude extract was caused by the cytolysin content. However, the reactions are identical qualitatively and are of the same magnitude.

Summary

A highly purified preparation of pneumococcal cytolysin was responsible for the corneal damage that ensued upon intracorneal injection of crude cell extract into the rabbit eye. The lysin may produce this pathologic finding by effecting activation or release of corneal degradative enzymes.

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MODIFICATIONS OF THE CONJUNCTIVODACRYOCYSTOSTOMY PROCEDURE

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Since the technique of conjunctivodacryocystostomy was reported in 1974,[1] several surgical modifications have evolved. I observed the original 12 patients (15 operations) and performed 28 additional operations (24 patients).

This procedure is not recommended as a substitution for the standard dacryocystorhinostomy. Hallum[2] and others have shown greater than 95% cure rate of epiphora with the Dupuy-Dutemps or modified dacryocystorhinostomy technique when at least the lower punctum and canaliculus are patent to the lacrimal sac. Conjunctivodacryocystostomy aids in proximal nasolacrimal drainage system blockages, and where dacryocystorhinostomies have failed or are not indicated.

SUBJECTS AND METHODS

The 24 patients (Cases 13-36) were similar to the 12 originally described[1] in that they all had injuries or diseases that obliterated the proximal portion of the nasolacrimal drainage system or had had previously unsuccessful dacryocystorhinostomies (Table).

The operation includes the original incision and exposure of the nasolacrimal sac and entrance to the duct. The periosteum along the anterior crest need not be excised unless necessary for aid in determining the entrance of the nasolacrimal duct into its bony canal.

A cataract knife was passed through the inferior cul-de-sac and subcutaneous tissues to the surgical space near the nasolacrimal duct entrance into its canal. A No. 3 or 4 Bowman probe (its grip or handle removed) was passed along the anterior surface of the cataract knife until its point was free of the orbicularis oculi muscle and other tissues over the nasolacrimal sac. I then removed the cataract knife.

I directed the probe into the bony canal with or without surgical incision of the sac or duct. I threaded the probe gently through the nasolacrimal duct into the anterior meatus until it rested on the nasal floor (not necessarily directly visible through the nares).

Previously flanged PE-190 polyethylene tubing, 45 mm long, was beveled and passed over the Bowman probe that was left in place. I gently threaded the tubing through the entire length of the probe to the nasal floor. The amount of tubing remaining above the point of entrance into the inferior cul-de-sac of the conjunctiva was measured and that exact amount plus 3 to 5 mm was excised from the end opposite the flanged end to allow the end to be suspended in the inferior meatus above the floor. The cut end should be beveled for easier passage over the tube through the tissues.

The prepared tube was rethreaded over the Bowman probe and, if no distal (nasal floor) resistance was met, the Bowman probe was carefully removed while gently holding the tube with forceps. The tube was irrigated with normal saline (with or without fluorescein added) to confirm patency. The nasal cavity was aspirated and the flanged end loosely sutured to the eyelid margin with a 6-0 black silk suture as previously described.

Since the nasolacrimal duct is 16 to 18 mm in length,[3] tubing longer than 30 mm was rarely used.

The PE-190 polyethylene tubing, which is available in 36-inch lengths, was prepared by cutting 5- to 6-inch lengths of individual

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TABLE

SUMMARY OF DATA

Case No., Age (yrs), Sex, Race	Diagnosis and History	Date of Surgery (mos since procedure)	Complications
1, 16, F, W	Auto accident with fractures, globe laceration, detached retina (dacryocystorhinostomy 7/70), LE	8/70 (51)	Tube plugged with debris, replaced 9/74 (49 mos)
2–12*	14 eyes, see original article[1]	Average, 31.3	1 tube rode up 1 mo postoperatively; shortened
13, 52, M, W	Chronic dacryocystitis (dacryocystorhinostomy twice), RE	12/72 (23)	None
14, 62, F, B	Trauma to globe, enucleation, chronic dacryocystitis (dacryocystorhinostomy 1970), LE	4/73 (19)	None
15, 56, F, B	Nonspecific eyelid inflammation with bilateral canalicular, blockage	Both eyes, 4/73 (19)	Tube replaced twice due to patient's refusal to self irrigate; now clean and functioning
16, 39, F, W	Chronic dacryocystitis for 15 yrs (dacryocystorhinostomy RE, 8/72; LE, 9/72)	LE, 3/73 (20) RE, 5/73 (18)	None
17, 19, M, W	Auto accident with severed canaliculi and fractured nasolacrimal duct, RE	6/73 (17)	None
18, 80, F, W	Chronic dacryocystitis with mucocele of sac (dacryocystorhinostomy 5/71), RE	6/73 (17)	Occasional conjunctival irritation on adduction, RE
19, 52, F, W	Idiopathic canalicular obstruction, RE	7/73 (16)	None
20, 53, M, W	Chronic dacryocystitis (dacryocystorhinostomy twice), RE	2/73 (21)	Original position of tubing was wrong (too nasal and high); repositioned 10/73
21, 52, M, W	Basal cell carcinoma, medial canthus excised 2/73; upper and lower puncti and canaliculi excised, LE	8/73 (15)	None
22, 31, F, W	Chronic dacryocystitis (dacryocystorhinostomy 1/72), LE	8/73 (15)	None
23, 53, F, W	Chronic dacryocystitis followed by occlusive scarring in medial canthus and canaliculi, RE	8/73† (6)	None
24, 66, M, W	Cyst excised from medial canthus (1958), punctal obliteration	8/73 (15)	Tube rode up; shortened
25, 43, M, W	Auto accident (1948), lacerated canthus with canalicular obstruction, RE	7/73 (16)	Granulation of conjunctiva over riding up of tube; excised and tube shortened
26, 54, M, W	Avulsed canaliculi (indwelling stints not effective)	8/73 (17)	None
27, 56, F, W	Lacerated medial canthus (blunt trauma) with canalicular obstruction, 1972, LE	10/73 (13)	Tube lost 11/73
28, 17, M, W	Congenital rubella with absence of all puncti and canaliculi, atresic sac	10/73 (13)	None
29, 33, F, B	Chronic dacryocystitis for 8 yrs, canalicular obstruction	10/73 (13)	None
30, 67, M, W	Severe periorbital thermal burns with occlusion, of all puncti	Both eyes, 11/73 (12)	None
31, 9, M, W	Dog bite, avulsed medial canthus and canaliculi, LE	1/74 (10)	None
32, 36, M, W	Caustic soda burns with cicatricial occlusion of all puncti	Both eyes, 2/74 (9)	None
33, 82, M, W	Chronic dacryocystitis (dacryocystectomy 1/64), LE	9/74 (2)	None
34, 11, M, W	Varicella induced canalicular scarring and occlusion, LE	10/74 (1)	None
35, 51, M, W	Carcinoma in papillary transitional cell and lacrimal sac (excised 6/74), RE	11/74 (1)	None
36, 29, F, I	Chronic dacryocystitis and mucocele lacrimal sac (dacryocystorhinostomy 1974), LE	11/74 (1)	Tube rode up 1 wk postoperatively; shortened

* Of these 11 patients, six were men, five were women, ten were white, and one was black.

† Patient died 1/74, acute myelomonocytic leukemia.

tubing. The cutting should be perpendicular to the outside wall of the tubing. The flanging can be accomplished over an open flame by using slow heat. Rapid heating will cause blistering or brittleness, or both. Practice makes this procedure simple. The tubes are individually packaged and gas sterilized.

The 36 patients (43 eyes), including 16 females and 20 males (Table), were observed for one to 55 months (average, 20.5 months).

Ages of the patients ranged from 9 to 82 years with a mean of 43 years.

Discussion

These modifications of the conjunctivodacryocystostomy technique simplify the original procedure. Occasional out-fracturing of the inferior turbinate may be done to give more room for entrance of the tubing but otherwise, no instrumentation of the nasal cavity is necessary. This has reduced the amount of occasional nasal mucous membrane bleeding considerably.

The diameter of the PE-90 tubing (interior diameter, 0.034 inches), in some cases, may be too small and harder to thread over a probe of sufficient size to force through the tissues. Hence, the PE-190 polyethylene tubing (interior diameter, 0.047 inches) is recommended.

To date, 43 conjunctivodacryocystostomies (36 patients) have been performed and only one severe complication has occurred, that is, loss of tube (Case 27).

Replacement of tubing can be performed in the office and this same technique can be used to shorten the occasional tube that "rides up" because of contact with the nasal floor. This complication does not occur if there is proper positioning at the time of surgery.

One to two drops of proparacaine hydrochloride is instilled into the inferior cul-de-sac and either a No. 3 or 4 or a No. 1 or 2 Bowman probe without handle is threaded down the tubing. The tubing is fixed by forceps at flange. The tubing is withdrawn over the probe and either replaced by flanged tubing of the same length, shortened or cleansed, and then replaced. The replacement over the probe has not been troublesome.

After several months of use, these tubes occasionally become plugged with inspissated mucous and must be replaced despite excellent hygiene.

The patient should clean the tubing weekly with water or saline and negative intranasal pressure (snuffing).

The ease with which these tubes are replaced suggests that an epithelialized fistula exists from the conjunctiva to and into the nasolacrimal duct. However, no patient has allowed us to leave the tubes out to prove this theory.

Summary

I modified the conjunctivodacryocystostomy procedure in 36 patients (43 eyes) by directly threading the pre-flanged PE-190 polyethylene tubing over a No. 3 or 4 Bowman probe into and through the nasolacrimal duct, contrary to the original intranasal maneuvers. This simplified the procedure but caused minor amenable complications such as shortening the tubing postoperatively. In eight of 43 eyes, replacement or shortening the tubing was easily done in the office over a handleless Bowman probe. In three of the 43 eyes, polyethylene tubing was occasionally plugged, requiring cleansing or replacement. Of the 43 tubes inserted, 42 are still in place and functioning.

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BRIEF HOSPITAL ADMISSIONS FOR PEDIATRIC STRABISMUS SURGERY

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The policy of performing certain elective pediatric surgical procedures on patients admitted briefly to the hospital has been the subject of recent reports.[1-4] These have been concerned with nonophthalmic surgical procedures. Others[5-11] have been concerned with the psychological factors involved in hospitalizing the child with strabismus. This is a retrospective study of strabismus surgery performed on children who were outpatients from March 1971 to July 1973. We included all those operated on as outpatients, clinic as well as private patients.

PATIENTS AND METHODS

We reviewed the charts of 170 consecutive patients who underwent strabismus surgery on an outpatient basis. No patients were excluded from the study for any reason. The charts were analyzed for the following factors: age, diagnosis, type of surgery, preoperative medication, type of anesthesia, anesthetic time (defined as the time between the induction of general anesthesia and extubation), recovery time (defined as the time between extubation and discharge from the hospital), and complications during induction, anesthesia, or recovery. We sent a questionnaire to the parents of all children. We attempted to tabulate the postoperative complications that ensued within the first 48 hours after surgery and that constituted part of the morbidity of the procedure. We also used this questionnaire to determine whether the parents had accepted their role in postoperative care. The success or failure of the various surgical procedures was not analyzed in this report.

Outpatient surgical routine—Surgery done on an outpatient requires few departures from the normal routine. Since such surgery was performed on Mondays only, the patients scheduled for surgery were seen in the clinic on Friday afternoon before the operation. History taking and physical examination were performed, blood and urine samples were drawn, and routine administrative procedures were completed. On Sunday morning the patients returned to the clinic and were examined by the anesthesiologists and ophthalmologists. At 6:45 AM on Monday, parents and child were assigned to a room on the general pediatric floor that served as a waiting and recovery room. No more than three patients and their parents were assigned to the same room. Surgery commenced at 8 AM and patients were operated on in order of increasing age. A nurse familiar with recovery room techniques supervised and was equipped with oxygen, suction, resuscitating drugs and equipment, and a telephone. After surgery and extubation, the child was returned to this room. When the nurse considered the child awake and ready for discharge, members of the ophthalmology and anesthesiology services examined and discharged the child. Parents were advised about possible serosanguineous drainage from the eye and on the eye pad; they were given aspirin and an antiemetic suppository; they were instructed in the use of simple arm restraints in smaller infants where necessary. The first follow-up visit was at 8 AM the next morning.

From the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, and Jackson Memorial Hospital, Miami, Florida. This study was supported in part by the Miami Beach Lions Club, and in part by the Heed Ophthalmic Foundation, Inc. (Dr. Weinstock).

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TABLE 1

DATA ON PATIENT POPULATION

Total No.	170
Male/Female	84/86
Age	
Mean	5.8 yrs
Range	5 mos–18 yrs
Diagnoses	
Esotropia	122
Exotropia	48
Strabismus repair	170
Primary	(151)
Reoperations	(19)

RESULTS

Patient population—The mean age of the patients was about 6 years (Table 1). We have avoided this type of hospitalization in older children because their size makes it difficult to restrain them under the limited recovery room circumstances should they have a stormy postoperative recovery period. Now the age limit is 10 years. We performed typical strabismus repair.

Types of anesthesia—Although surgery was performed on an outpatient basis, most patients received the same type and dosage of preoperative medication as inpatients (Table 2). We preferred mask as the usual method of induction of anesthesia to the trauma of a needle puncture. For the occasionally objecting child, we administered a small dose of intravenous thiopental sodium (Pentothal). In all cases the airway was maintained via endotracheal intubation. A combination of halothane, nitrous oxide, and oxygen was used as the anesthetic agent in all cases. Anesthesia averaged 91 minutes (Table 3). This may seem long, but two factors account for this: First, this was a teaching situation involving both anesthesiology and ophthalmology residents. Second, 32% of the muscle procedures were performed on three or more muscles and 11% were reoperations. The few anesthesia complications (Table 4) occurred from traction on the rectus muscle during surgery.[12] No greater risk of intraanesthesia complications seemed to exist for the outpatient as compared with hospitalized patients.

Anesthetic variables—Several factors affecting the course of surgery on an outpatient basis may be partially controlled by the surgeon-anesthesiologist team. We tabulated data on the incidence of various preoperative medication regimens and the length of exposure to anesthetic gases against the occurrence during postoperative recovery of nausea, vomiting, drowsiness, eye pain, cough, croup, and chest pain. To determine the influence of each factor on the incidence of these postoperative symptoms, we performed many chi-square tests using these data.[13] Of these, only the type of preoperative medication used caused postoperative vomiting in a manner that differed significantly from chance (Table 5). Atropine alone was accompanied by less nausea and vomiting than any other anesthetic drug employed. With this regimen, less than one child in five was likely to have postoperative vomiting, while the addition of agents such as a narcotic, barbiturate, or tranquilizer in-

TABLE 2

PREOPERATIVE MEDICATION

Medication	No. of Patients	% of Total
Atropine	31	18
Atropine and meperidine	107	63
Atropine and pentobarbital*	10	6
Atropine and meperidine†	18	11
None	4	2

* Diazepam or droperidol occasionally used instead of pentobarbital.

† Pentobarbital, or secobarbital, or diazepam used occasionally instead of meperidine.

TABLE 3

DURATION OF ANESTHESIA

	Time, min	No. of Patients
	– 60	6
	75	33
	90	49
	120	67
	+120	15
Range	40–170	
Average	91	

creased the risk of postoperative vomiting. With the vomiting there is a risk of aspiration, and postoperative vomiting was an important reason for parental dissatisfaction with the scheme of surgery on outpatients.

Other trends in our data did not reach the level of statistical significance. For example, patients receiving atropine alone seemed more likely to require aspirin for postoperative pain (the only analgesic used in this study) than if they had received meperidine (Demerol) or a barbiturate before anesthesia; and prolonged drowsiness seemed to occur more frequently in patients who ingested atropine and either a barbiturate or a narcotic rather than atropine alone.

Recovery time—Our anticipation was that prolonged recovery would be associated with the longer surgical procedures. This was not the case. The statistical data seemed to show a wide range of recovery time that averaged about four hours. When we examined the data more closely, we found that a factor governing the length of recovery time was the availability of the physician to observe the patient after surgery. This meant that patients who were operated on early in the day waited until the surgeon and anesthesiologist completed all scheduled operations, although the patients might be awake and ready for discharge. In contrast, those operated on later in the day had shorter recovery times since the surgeon was usually available to discharge them.

Postoperative complications—In addition to 85 patients with postoperative vomiting, 21 had pain requiring aspirin, seven had prolonged drowsiness while recovering from anesthesia, two developed croup, and one developed fever. Although several of these complications were potentially serious, none resulted in a major complication. All but eight patients were discharged on the day of surgery. Of the eight patients who remained overnight, all were discharged the next morning. Two of the eight patients stayed because of the late hour at which anesthesia wore off. Two patients had croup that responded to a croup tent while the other four had prolonged drowsiness. This number might be reduced by a judicious choice and dosage of medication before anesthesia.

TABLE 4

INTRAANESTHESIA COMPLICATIONS (4.6%)

Complications	No. of Patients	Treatment
Bradycardia	3	Atropine
Premature ventricular contractions	3	Atropine*
Other arrhythmias	2	Atropine

* One patient received retrobulbar injections of lidocaine.

TABLE 5

POSTOPERATIVE VOMITING*

Preoperative Medication	No. of Patients Receiving Medication	No. of Patients With Vomiting
Atropine	31	6
Atropine and meperidine	107	68
Atropine and pentobarbital†	10	4
Atropine and meperidine‡	18	7

* Chi-square test, 20.356; $P < .001$; and degrees of freedom, 3.

† Diazepam or droperidol were occasionally used instead of pentobarbital.

‡ Pentobarbital, secobarbital, or diazepam were occasionally used instead of meperidine.

Subjective data—We received questionnaires from 67 parents (Tables 6 and 7). We have no means of assessing the attitude of those who did not reply. The parents were asked not to identify themselves in the hope that anonymity would encourage candor and increase the number of replies.

Specifically, we sought information regarding the following symptoms on discharge from the hospital: state of wakefulness, eating and drinking, crying, vomiting, pain, and the like, and whether these symptoms recurred within the first 48 hours. To gauge how disturbing any of these symptoms were, we asked the parents to specify whether they would have preferred an overnight stay

TABLE 6

CONDITIONS AT DISCHARGE*

Symptoms at Discharge	Positive Response	No. Replying to Question	% of Positive Responders Wanting Overnight Hospitalization
Fully awake	26	58	15
Eating	15	53	27
Drinking	24	49	37
Sleeping fitfully	37	58	49
Sleeping	13	51	77
Crying abnormally	10	51	70

* Data tabulated from 67 responses to parental questionnaires.

in the hospital for their child. If the child was awake, eating, and drinking before discharge, the experience was a positive one for most respondents (85%). If, however, the child was sleeping fitfully or full-time, crying or crying abnormally, vomiting or in pain, most parents would have preferred that these symptoms be dealt with by hospital personnel.

DISCUSSION

The procedure itself, as far as we are concerned, is safe and practical for children with strabismus. It is also probably safe for patients with congenital cataracts, glaucoma, and blepharoptosis. We are slowly adding these procedures as our familiarity with this type of surgery grows. Patient selection is most important. If the parents are hesitant to accept care of a drowsy, sick, or crying child, this patient should not be accepted as an outpatient.

We discovered that the patient must live within a 20-mile radius of the hospital because the ride home is often a trying experience when the distance is longer. These patients should also be discharged before the rush-hour. For parents who live more than 20 miles from the hospital, we insist that they engage a motel room within walking distance of the hospital. We have learned to spend more time with the parents regarding the routine and with the child, explaining what may be expected. If we give a thorough explanation, the parents and the child more readily accept the difficulties involved in the procedure.

As to the routine itself, we recognize the main weakness to be the combination waiting and recovery room we were forced

TABLE 7

CONDITION AFTER DISCHARGE*

Symptoms Within 48 hrs	Positive Response	No. Responding to Question	% of Positive Responders Wanting Overnight Hospitalization
Drowsiness	17	64	82
Abnormal crying	10	60	60
Eye pain	38	61	47
Vomiting	29	66	59
Difficulty eating	19	61	68
Fever	14	62	57
Cough, croup	6	60	50
Sore throat, chest pain	5	6	80

* Data tabulated according to 67 responses to parental questionnaires.

to use because of a critical bed shortage in the pediatrics section. A child recovering from anesthesia may adversely affect the morale of other children and their parents. Although we used screens and discreet placement, we could not completely counter this effect. The ideal situation is a suite of three rooms: a waiting room adjoining an induction room where the parents could be with the child during anesthesia; an adjoining operating room; and a recovery room where the parents could stay with the child until discharge. We hope to implement this arrangement in the future.

Regarding the surgical routine, a good explanation allays the child's anxiety and atropine best reduces the incidence of postoperative vomiting. The child who receives only atropine preoperatively is awake sooner and seems to have less postoperative morbidity except for eye pain. Intubation is a safe procedure and should be employed in this type of surgery for the safety of the child. When the child is discharged the same day and has received only atropine, gentle and careful intubation is necessary. Close cooperation and understanding between the surgeon and the anesthesiologist is essential. The anesthesiologist must be fully aware of the aims of this type of surgery and must exercise care in choosing medication and the type of induction.

Although overnight facilities should be available to patients who require them, it is also important to discharge the patients when they are ready. Someone may have to leave the operating room to do so, but when these children are ready, they should be discharged immediately. This contributes to making this an acceptable experience to the child and parents.

Summary

We performed strabismus surgery on 170 children on an outpatient basis. Endotracheal intubation was utilized in all cases as the means of delivery of the anesthetic agent. Atropine used alone as a preoperative medication reduced the incidence of postoperative vomiting. Parental acceptance of this method of surgery was best when the child was discharged from the hospital awake and alert in the shortest possible time.

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AUTOTRANSPLANTATION OF RETINAL PIGMENT EPITHELIUM IN INTRAVITREAL DIFFUSION CHAMBER

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A typical feature of eyes with experimental retinal detachment is the proliferation of cells in the posterior part of the eye. These cells act as macrophages and form membranes, causing retinal folds and vitreous strands. Histologic and electron microscopic studies led to the hypothesis that many of the cells derive from transformed retinal pigment epithelial (RPE) cells.[1]

The purpose of this experiment is to confirm the capability of RPE cells to transform into macrophages and strand-forming cells. Retinal pigment epithelial cells from one eye are transplanted into the vitreous cavity of the other eye. To avoid any contamination of the RPE cell culture the cells are placed in diffusion chambers. Diffusion chambers are cell impermeable, but allow fluids to pass through the small pores.[2,3]

MATERIALS AND METHODS

Construction of diffusion chambers—Lucite rings (outer diameter: 7 mm; inner diameter: 4 mm; height: 2 mm) with a 1-mm radially oriented filling hole were soaked in petroleum-ether for 48 hours, washed in detergent solution, rinsed in distilled water, and dried at 60°C. Millipore filter disks of 0.22 μ pore size punched to 6 mm diameter were then glued by MF-cement on both sides of the lucite ring. To assure cell-tight sealing, the glue was applied again after one hour to the outer edge of the filters.[4] After gas-sterilization, the chambers were soaked in Hanks' balanced salt solution containing 2% rabbit serum for 48 hours to remove toxic remnants of glue and ethylene oxide.

Harvesting of the RPE cells—Twenty-four pigmented rabbits, weighing between 2 and 4 kg, were used. Under general anesthesia with intraperitoneal pentobarbital (Nembutal) the right eye was enucleated. For stabilization of the globe, a metal ring was fixed to the sclera posterior to the corneoscleral limbus by using a running 5-0 nylon suture. The anterior segment was removed slightly behind the ora serrata. By utilizing a stream of saline solution we gently detached the retina from the RPE and then cut it from the optic disk. After washing the remainder of the globe three times with saline to eliminate any free-floating cells it was filled with a 0.25% trypsin solution and incubated at 37°C for 30 to 40 minutes. This loosened the attachments between the RPE cells and Bruch's membrane so they could easily be aspirated with a blunt 18-gauge needle under the operating microscope.[5] Bruch's membrane was left intact, as proven by examination under 40× magnification. The cell suspension was placed in a 5-ml conical tube and washed by centrifugation (1,000 rpm for four minutes) three times in Eagles minimum essential medium con-

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This investigation was supported in part by Public Health Service research grant EY-00841 from the National Eye Institute; in part by the Veterans Administration Hospital, Miami, Florida; in part by Research to Prevent Blindness, Inc., New York City; in part by the Florida Lions Eye Bank, Inc., Miami, Florida; and in part by the Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg, Germany. Dr. Mueller-Jensen is a visiting research fellow from the University Eye Clinic, D8, Munich, Germany.

Presented in part at the Ninth Meeting of the Club Jules Gonin, LaBaule, France, May 12-18, 1974.

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taining 2% rabbit serum to inactivate all trypsin.

The centrifuged RPE cells were aspirated into a fine glass pipette and injected into the diffusion chamber. The filling hole was closed by a drop of liquid paraffin and then covered with MF-cement. The complete chamber was placed into Eagles minimum essential medium for several minutes during which the other eye was prepared for implantation of the chamber. The chamber was carefully introduced into the vitreous cavity of this eye through a 9-mm incision near the ora serrata which was closed by four preplaced 5-0 nylon sutures.

To examine DNA-synthesis of the transplanted cells, 50 μCi of tritiated thymidine with a specific activity of 5.0 curie/mM was injected through the pars plana two hours before enucleation. The chambers were removed at one, three, and seven days, and two, four, and nine weeks after implantation and fixed in 6% buffered glutaraldehyde (pH 7.3) for 24 hours. The contents of the chambers were postfixed in 2% osmium tetroxide for one hour, dehydrated, and embedded in Epon.[6] One-micron sections of the specimens were alternately stained with paraphenylenediamine for phase contrast microscopic evaluation or used for autoradiographic evaluation, for which they were coated with Kodak NTB-2 emulsion (diluted 1:1 with distilled water at 40°C). After exposure of the coated slides in the presence of a desiccant at 4°C for five days they were developed with Kodak D-19 developer (63 g in 550 ml distilled water) at 18°C for four minutes and fixed in sodium thiosulfate for ten minutes.

After light microscopic evaluation, characteristic areas were chosen and cut as ultrathin sections (0.05 μ) from the same block to correlate histology and fine structure of a given cell. The thin sections were stained with uranyl acetate and lead citrate and examined with a JEM-7 electron microscope.

In control experiments part of the cells collected were examined histologically for possible contamination. To verify that the sealed chambers were cell-tight, empty chambers were implanted intravitreally for ten days into eight rabbit eyes. The Millipore cells were examined histologically. Also, in vitro cell cultures were obtained from four eyes to study the purity of the obtained cell population.

Results

The operated eyes tolerated the large chambers well (Fig. 1). Macroscopically, up to seven days, there were no significant changes inside the diffusion chambers. Usually round pigment clumps were seen. After two weeks an outgrowth of tissue was observed after which there was an increasing amount of strand and membrane formation (Fig. 2). The newly formed tissue was less and less pigmented.

By light microscopy in the first week there were isolated round, oval, or wedge-shaped cells containing ellipsoid-shaped pigment granules typical of RPE. After two weeks the cells were more spindle shaped. Some free pigment granules and debris were visible. Between four and nine weeks the spindle-type of cells predominated (Fig. 3). Most of the cells now appeared pigment-free and the debris observed in the earlier stages was markedly decreased.

By electron microscopy three days after intravitreal implantation, single usually round cells were seen containing ellipsoid and round pigment granules, most of which were found free in the cytoplasm and not in phagosomes. The cytoplasm was full of lipoid material and some lameller inclusion bodies were also found (Fig. 4). Microvilli were seen to protrude from the cytoplasm. After one week the surviving cells contained fewer pigment granules, started to become spindle shaped, and demonstrated intercellular connections such as desmosomes. After two weeks and, up to nine weeks, collagen fibrils with a periodicity of about 60 nm and a diameter of about 25 nm were found between the cells.

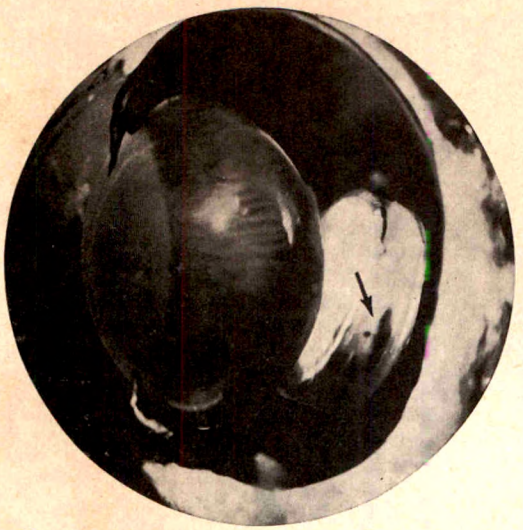


Fig. 1 (Mueller-Jensen, Machemer, and Azarnia). Glutaraldehyde-fixed rabbit eye with diffusion chamber in situ four weeks after implantation. Pigmented tissue (arrow) is seen within the chamber through the transparent lucite ring.

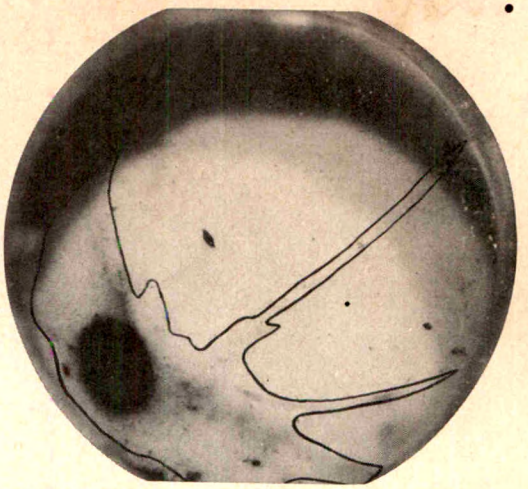


Fig. 2 (Mueller-Jensen, Machemer, and Azarnia). A clump of pigmented tissue in the opened chamber. The black line outlines the finger-like extensions of proliferated tissue.

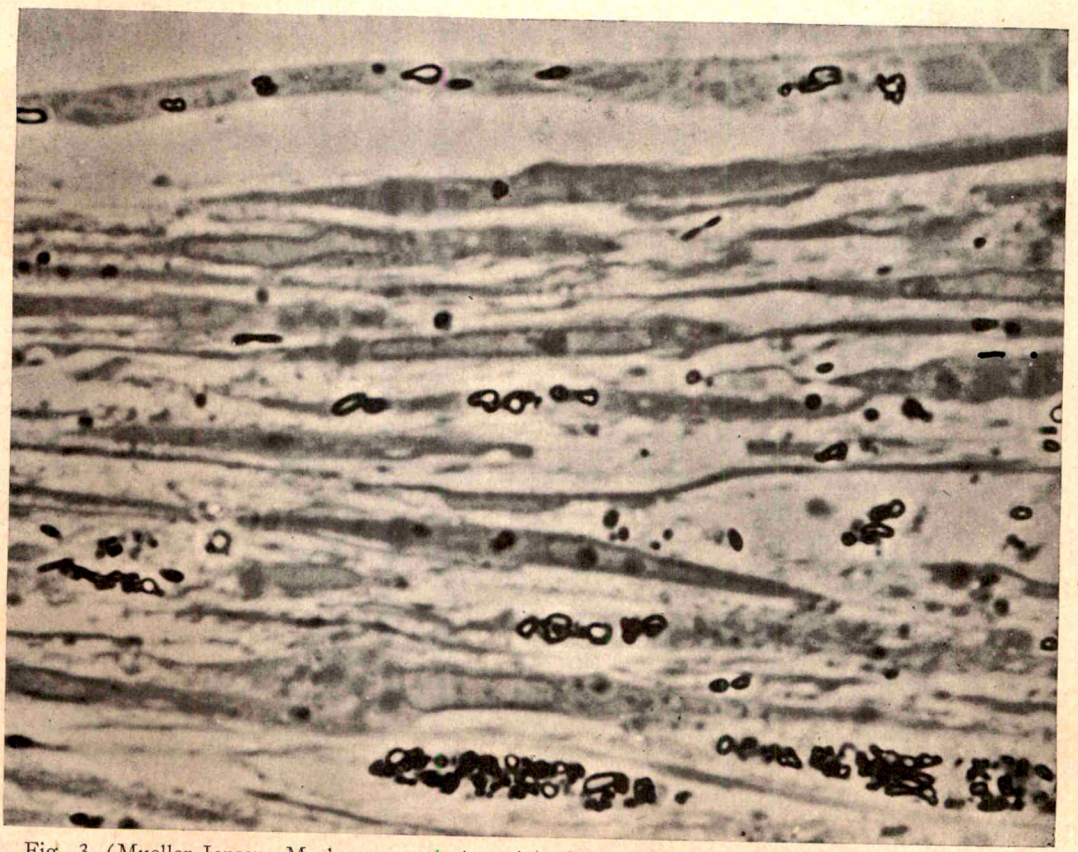


Fig. 3 (Mueller-Jensen, Machemer, and Azarnia). Metaplastic hypopigmented spindle-shaped RPE cells four weeks after autotransplantation in a diffusion chamber (paraphenylenediamine stain, phase contrast, ×1,000).

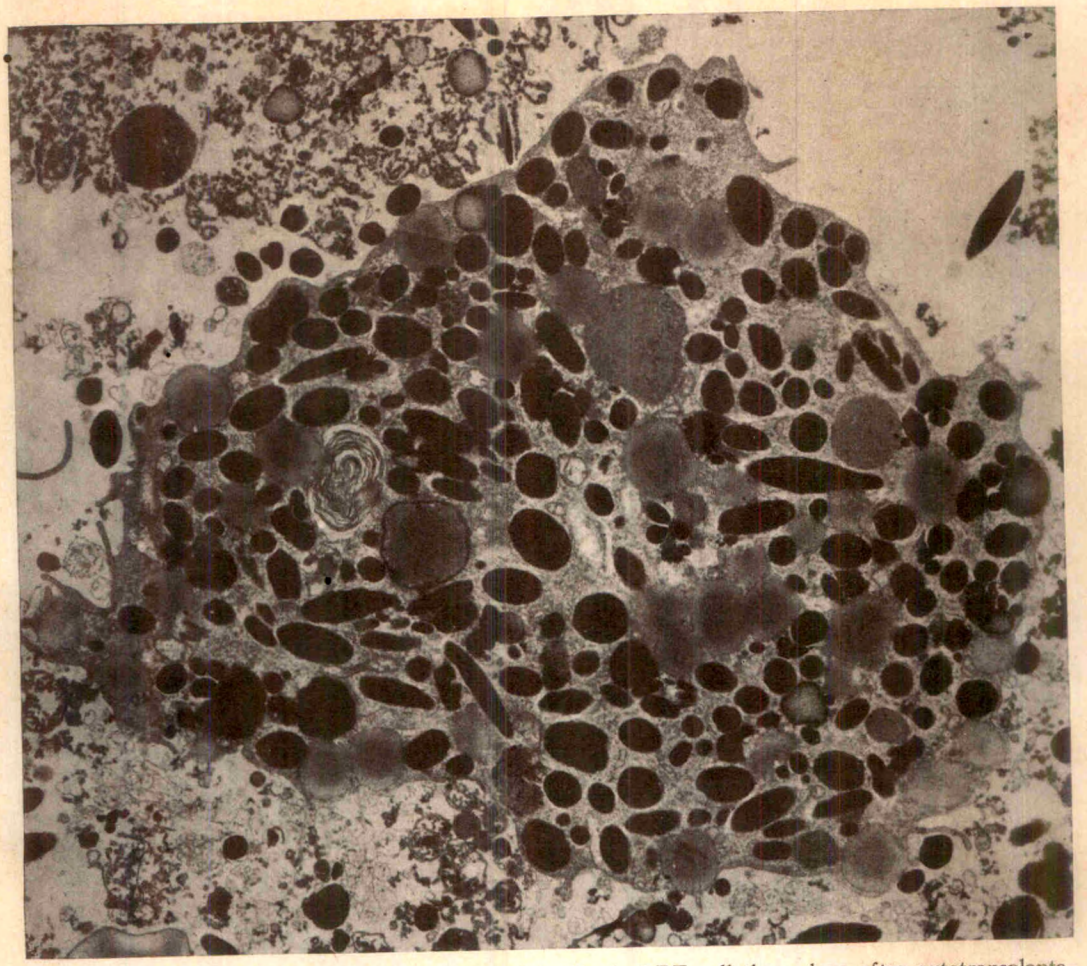


Fig. 4 (Mueller-Jensen, Machemer, and Azarnia). Single RPE cell three days after autotransplantation containing free ellipsoid and round pigment granules, much lipoid material, and a lameller inclusion body. Debris around this cell probably derives from disintegrated RPE cells (×8,500).

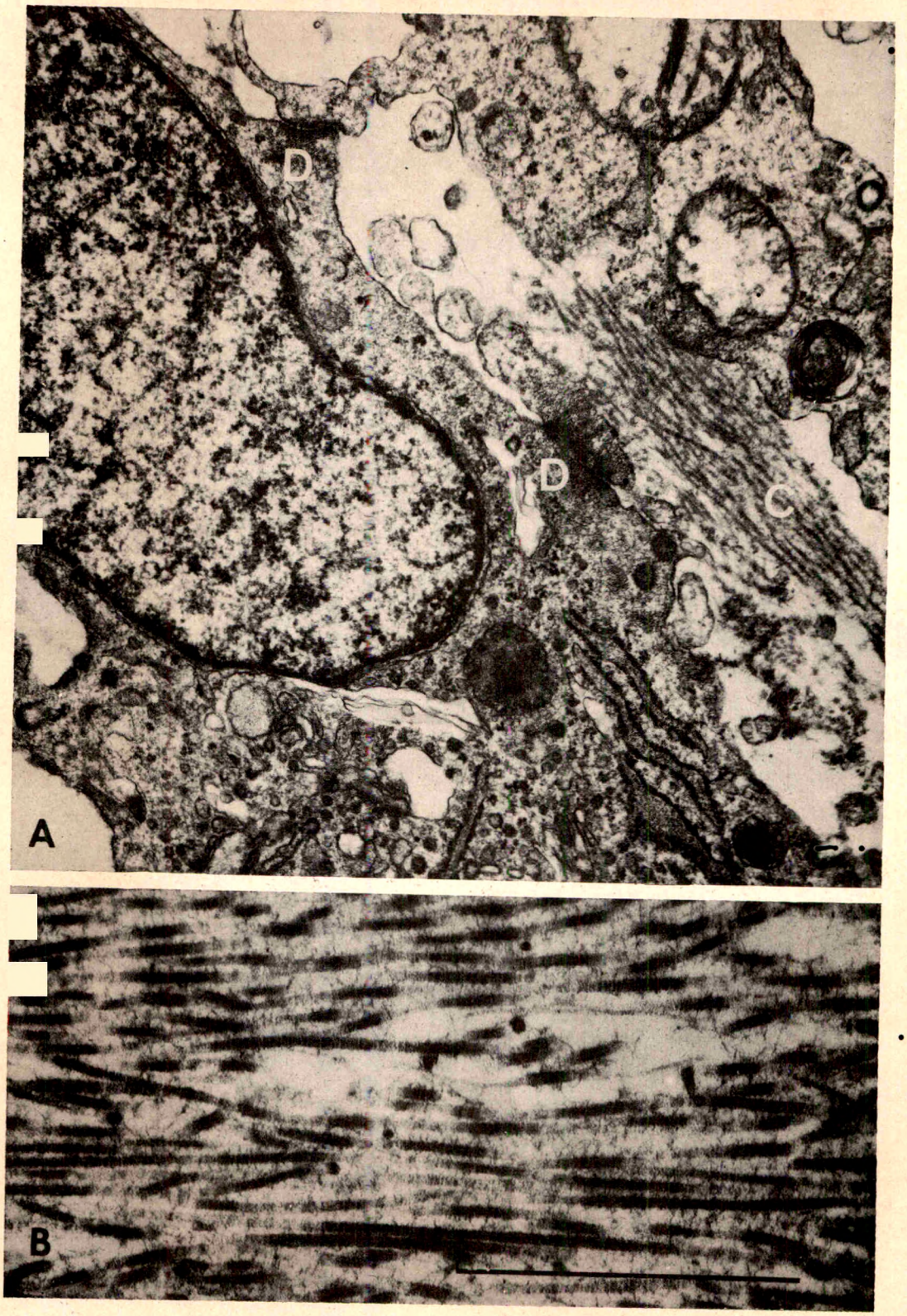
The amount of collagen increased with time (Fig. 5).

Autoradiography demonstrated DNA uptake at one, two, four, and nine weeks (Fig. 6).

The control experiments showed that the collected cells examined histologically showed a pure pigment epithelium population. The eight empty chambers implanted for ten days and examined histologically did not show any cellular ingrowth. In vitro cell cultures showed no contamination of the collected RPE cells. A uniform population of spindle-shaped cells which became less and less pigmented over a period of nine weeks was found.

Discussion

Histologic and electron microscopic studies of eyes with experimental retinal detachment,[1] as well as experiments with autotransplantation of RPE cells into the vitreous cavity,[7] strongly suggest that part of the proliferating tissue in the posterior part of the eye derives from the pigment epithelium cells. This experiment was designed to isolate pigment epithelial cells, eliminate any contamination, grow them, and study their inherent metaplastic capabilities. The experiment demonstrates that it is possible to isolate pure pigment epithelium population. Neither histologic study of the cells harvested from the other eye nor in vitro cell


D
D
C
A
B

cultures revealed any contamination with other cells. The diffusion chambers themselves are absolutely cell-tight. Macroscopic and histologic examination of empty diffusion chambers placed into the eye did not show any cell inside the chamber. The use of the diffusion chambers therefore permits isolation of a specific cell type and its growth in a natural environment. No better medium to nourish the isolated RPE cells can be thought of than the living eye.

The study of the cell in the diffusion chamber shows as a first step the transformation of the RPE cell into a macrophage, with microvilli, filled with phagocytosed material. The only reminders of the RPE origin are the many wedge-shaped pigment granules. Almost all pigment granules are free within the cytoplasm, indicating that they have not been phagocytosed. An occasional lamellar inclusion body may be the remnant of phagocytosed outer segment material at the time when the cell was still in contact with the outer retina.[8] The typical feature of the RPE cell—basement membranes and connection of the cells to each other by junction complexes—is not found in these cells.

The fact that much cellular debris is found between living cells indicates that obviously

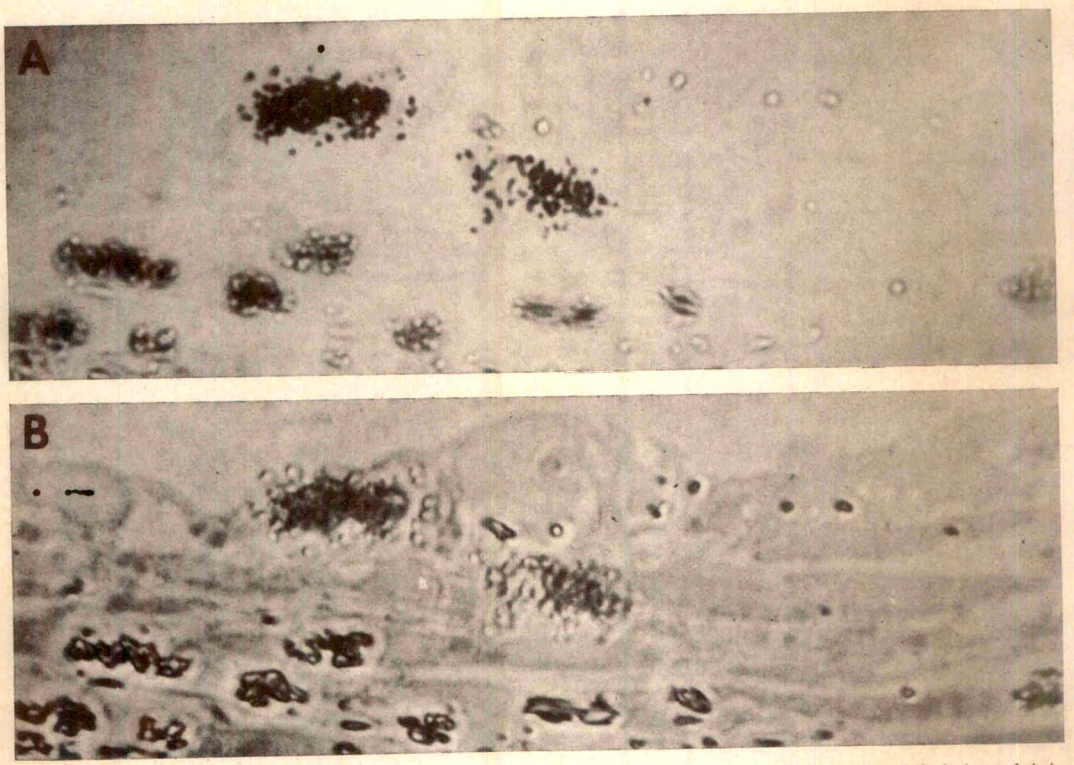


Fig. 6 (Mueller-Jensen, Machemer, and Azarnia). Autoradiography of thymidine-labeled nuclei in proliferating RPE cells. Upper and lower photographs show identical areas of the specimen; A focuses on the silver grain, B focuses on cells (unstained, phase contrast, ×1,000).

←

Fig. 5 (Mueller-Jensen, Machemer, and Azarnia). A, Epithelial cell characteristics of the metaplased spindle-shaped cells four weeks after autotransplantation: two cells connected by desmosomes (D). Note the collagen (C) between the cells (×26,000). B, Higher magnification of this collagen demonstrates a periodicity of 60 nm. Bar gauge = 1 μ (×54,000).

not all cells have survived the transplantation.

By the second week a second transformation takes place. The previously more round or irregularly shaped cells assume a spindle shape and form coherent membranes. These cells regain epithelial cell characteristics and are now connected to each other by cell junctions. The fact that these cells have epithelial cell characteristics is an additional argument against contamination of the cell cultures in the chambers with other cells. Fibrocytes, histiocytes, or blood macrophages which are of mesodermal origin and which could have contaminated the chambers usually do not form cell junctions.

The spindle-shaped cells are surrounded by collagen. Collagen contamination from the vitreous can be excluded since vitreous collagen has a different periodicity (22 nm)[9] than the collagen found in the chamber (60 nm). One must therefore conclude that this collagen has been produced by the spindle-shaped cells themselves. Collagen formation of RPE cells is not unknown. It has been shown that chick embryo RPE cells in vivo and in vitro can produce collagen.[10] In plaques of proliferating RPE cells overlying malignant choroidal tumors in man,[11] and in photic maculopathy in monkeys,[12] collagen fibrils with a periodicity of 60 to 70 nm were observed.

It appears therefore that RPE cells are capable of a de-differentiation into macrophages with loss of epithelial cell characteristics. A re-differentiation occurs when these cells are transformed into strand-forming epithelial cells with collagen production. As has been discussed in a previous paper,[1] we would like to call this first type of cells pigment epithelial macrophages[13] to avoid confusion with macrophages of other origin. The strand-forming cells have histologic similarity to fibrocytes but are definitely different from these because of their epithelial cell characteristics. Therefore, we call these cells fibrocyte-like cells.

The fact that labeled cells were found after tritiated thymidine application demonstrates active proliferation of the cell culture. Thymidine is used in the process of DNA replication. DNA replication usually means that a cell is preparing for mitosis. Since no mitoses were found, multiplication of DNA without mitosis (polyploidy) cannot be fully excluded. The decreasing pigmentation of the proliferating cells both in vitro and in vivo suggests cell division, because in RPE cultures cell pigmentation and cell proliferation appear to be two mutually exclusive phenomena.[14] This loss of pigmentation in RPE cultures was also observed by other authors.[5,15,16]

The results of this experiment support the hypothesis that experimental retinal detachment macrophages and strand-forming cells that participate in the development of massive periretinal proliferation[1] derive from RPE cells.

Summary

Retinal pigment epithelial (RPE) cells were autotransplanted intravitreally in diffusion chambers in rabbit eyes. The RPE cells underwent transformation; first into macrophages, later into spindle-shaped cells with collagen production having epithelial cell characteristics.

DNA replication, shown by autoradiography, and loss of pigment granules indicated proliferation of these cells. These results support the hypothesis that RPE proliferation and transformation play a major role in the formation of collagen containing membranes, such as are found in massive periretinal proliferation.

Acknowledgments

We thank Douglas R. Anderson, M.D., for assistance in electron microscopic interpretation; Mrs. Marcilia Halley, Mr. Barry Davis, Mr. Willi Aumayr, and Mr. Ernest Reeves for technical assistance; Mr. Wayne Hinecker for his help in the animal experiments; William Benson, M.D., for editorial assistance; and Mrs. Charlaine Rowlette for secretarial assistance.

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CATARACTS IN BLEOMYCIN-TREATED RATS

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Bleomycin (Blenoxane) is a recently developed chemotherapeutic cancer agent. Umezawa and associates[1-3] first isolated the drug from *Streptomyces verticillus*. Its structure includes sulfur-containing basic peptides, with 1,400 mol. wt. Screening studies showed that in addition to a bactericidal effect on *Escherichia coli*, this antibiotic had an antitumor effect on canine lymphosarcoma. Further investigations determined that the drug concentrated in epidermal tissues, particularly in those producing keratin.[4] Later clinical studies showed bleomycin was particularly beneficial in the treatment of squamous cell carcinoma of the head and neck, lymphosarcoma, Hodgkin's disease, and embryonal cell carcinoma of the testis.[5-8]

Reported toxic and side effects include interstitial pneumonia, pulmonary interstitial fibrosis, skin rashes, stomatitis, mucositis, digital gangrene, systemic sclerosis, anaphylaxis, nausea, anorexia, weight loss, fatigue, and headache.[4-6] Bleomycin has no depressing effects on the bone marrow or gastrointestinal epithelium.[7]

While evaluating the effect of bleomycin on the growth of human cancer growing as a heterotransplant in immunologically tolerant rats,[9] we observed that some of the treated experimental rats had developed a peculiar cloudiness of the ocular media. We designed a study to determine the relationship of bleomycin and the experimental cancer to the development of these opacities.

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The tumors used in this system originated from the human cell line designated J-111 which was originally isolated from blood buffy coat of a patient with leukemia.[10] The antitumor aspects of this study are not pertinent to the present report but have been previously reported.[11]

METHOD

Newborn white Fisher rats were given an intravenous injection of 2×10^6 cells of human cancer cell line J-111 on the day of birth and received bleomycin at various ages. Other litter mates were not given tumor cells but were treated with bleomycin on the same schedule. The earliest treatment was at 3 days old and the latest was begun at 15 days. The dosage of bleomycin was 0.5 units per kilogram of weight, administered intraperitoneally. The average weight of a newborn rat was about 8 g. One hundred eight rats were given both bleomycin and tumor cells while 18 received only bleomycin. Another 15 rats received neither bleomycin nor J-111 tumor cells and served as controls. The animals were observed for ophthalmoscopic changes by using the slit-lamp biomicroscope and a dissecting microscope. Several eyes were enucleated at varying intervals after development of opacities and examined histologically. Our goal was to determine the nature of these opacities and whether their development could be attributed to the bleomycin administration alone.

RESULTS

The eyelids of newborn rats were structurally fused for 12 to 14 days when they were surgically separated to permit ophthalmoscopic inspection. Examination of rats during this period from both the treated and the untreated groups did not reveal any



Fig. 1 (Edwards and associates). Bleomycin-treated rat with cataract.

opacities in the ocular media. Initial changes in the lenses of 14- to 16-day-old rats consisted of nuclear and perinuclear opacities. For one to two weeks, these opacities progressed into a dense white irregular cataract with feathery borders, sparing only the outer 10% of the lens cortex (Figs. 1 and 2). All the cataracts were bilateral and developed only in bleomycin-treated rats. The development of cataracts apparently was not related to the administration of the J-111 tumor cells; rats receiving only bleomycin also developed lens opacities. Less cataract formation occurred at the age in which bleomycin was increased. No cataracts developed when the drug was administered ten or more days after birth (Table, Fig. 3).

We examined the enucleated eyes histologically including those with early nuclear opacities as well as those with dense total cataracts. The earliest nuclear opacities, which were grossly obvious, could not be differentiated from normal lenses histologically (Fig. 4). In the more advanced

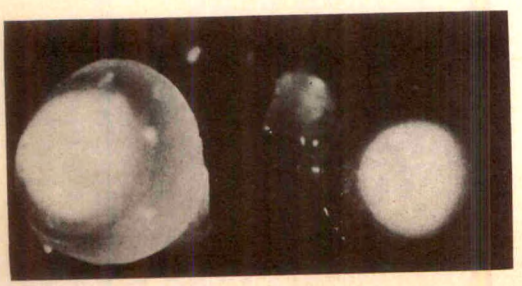


Fig. 2 (Edwards and associates). Enucleated eyes with almost complete cataract treated with bleomycin.

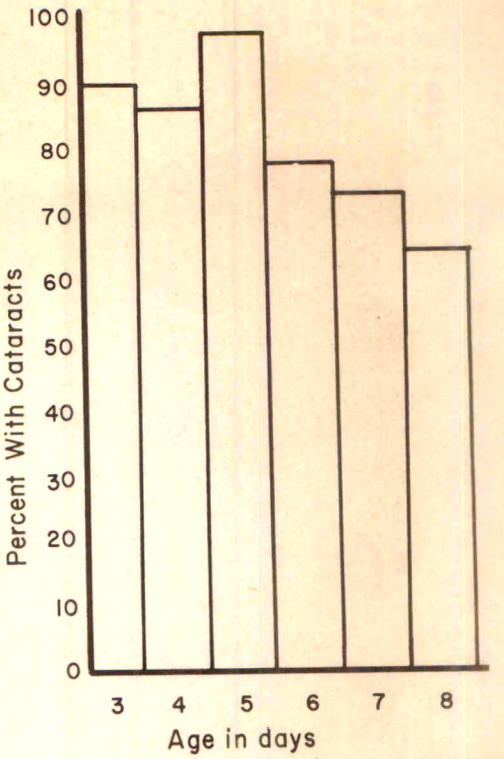


Fig. 3 (Edwards and associates). Percentage of rats developing cataracts after treatment with bleomycin started at different ages.

cataracts, however, posterior epithelial migration, loss of epithelial cells, cleft formation, bladder cell formation, and cortical liquefaction became evident (Fig. 5). In rats who received the J-111 tumor, neoplastic cells were sometimes observed in the vitreous cavity, the anterior chamber, and the iris surface. Blood vessels were also seen in the vitreous cavity and around the lens in eyes removed from rats younger than 10 to 12 days old (Fig. 6). These vessels are probably part of the hyaloid vascular system.

Discussion

The development of lens opacities following treatment with many cancer chemotherapeutic agents is not new. Busulfan (Myleran), mechlorethamine hydrochloride (nitrogen mustard), triethylenemelamine, 4-paradimethylaminostyryl-quinolone, mimosine, and cyclophosphamide have caused cataracts in experimental animals.[12-18] How-

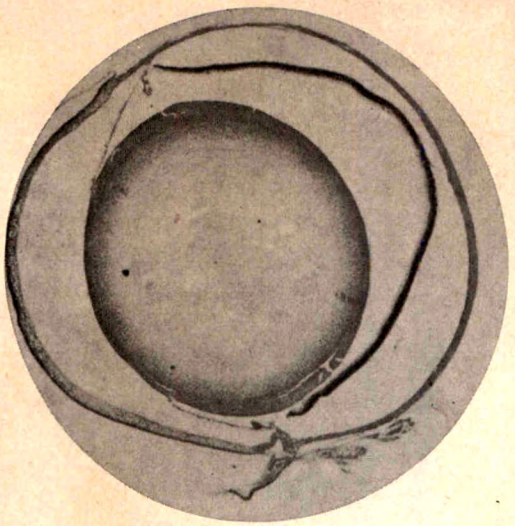


Fig. 4 (Edwards and associates). Section of eye with clinically obvious central cataract. Minimal histologic changes.

ever, cataract formation during bleomycin therapy has, to our knowledge, not been reported either in human patients or in experimental animals.

Bleomycin is known to inhibit DNA synthesis and concentrates on newly formed or proliferating, epidermally derived tissue. Because of the particular localization of this drug, its initial use was for epidermal malignancies and, in particular, squamous cell carcinoma.

The crystalline lens is an epidermally derived structure in which a continuous formation of lens fibers from equatorially located cells occurs throughout life. Because of the known action of bleomycin, we anticipated at the outset that the earliest lenticular changes would occur on the equatorial cells and equally affect both young and old rats. Our results failed to prove these theories. Grossly visible lenticular opacities, nuclear in location, antedated the appearance of histologic changes in the equatorial cells. Furthermore, bleomycin did not cause cataracts in rats older than 10 days. Therefore, this drug appears to induce the formation of cataracts through a mechanism other than a direct cytopathic effect on growing lens cells. The nondevelopment of cataracts in older rats may be related to the regression of the hyaloid vascular system that occurs at approximately ten days.[19] Possibly, the disappearance of these vessels results in a diminished ocular concentration of bleomycin and failure to induce cataracts. There is no apparent reason, however, to explain why the initial lens opacities are centrally rather than peripherally located.

Summary

Bleomycin was administered to 126 normal or human-tumor-bearing baby rats we

TABLE

CATARACT FORMATION AFTER BLEOMYCIN TREATMENT

Age at Bleomycin Administration, days	No. of Developing Cataracts/No. Treated with J-111 and Bleomycin	Rats with Cataracts, %	No. of Developed Cataracts/No. of Rats Treated with Bleomycin	Rats with Cataracts, %	Total Rats with Cataracts, %
3	7/8	87.5	2/2	100	90
4	16/18	88.8	0/0	0	88.8
5	14/14	100.0	7/8	87.5	95
6	18/23	78.0	0/0	0	78
7	9/12	75.0	2/3	66	73
8	4/4	100.0	0/2	0	66
10	0/4	0	0/0	0	0
11	0/8	0	0/0	0	0
12	0/4	0	0/3	0	0
13	0/13	0	0/0	0	0
14	0/12	0	0/2	0	0
15	0/13	0	0/1	0	0

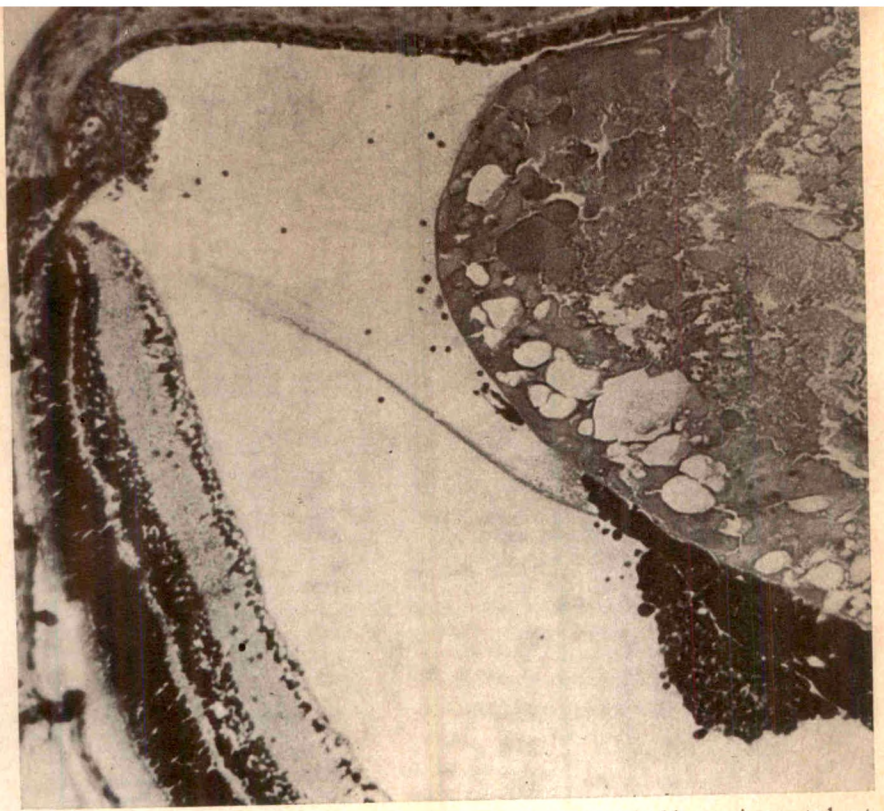


Fig. 5 (Edwards and associates). Advanced total cataract in bleomycin-treated rat. Note J-111 tumor cells on posterior lens capsule (hematoxylin and eosin, ×80).

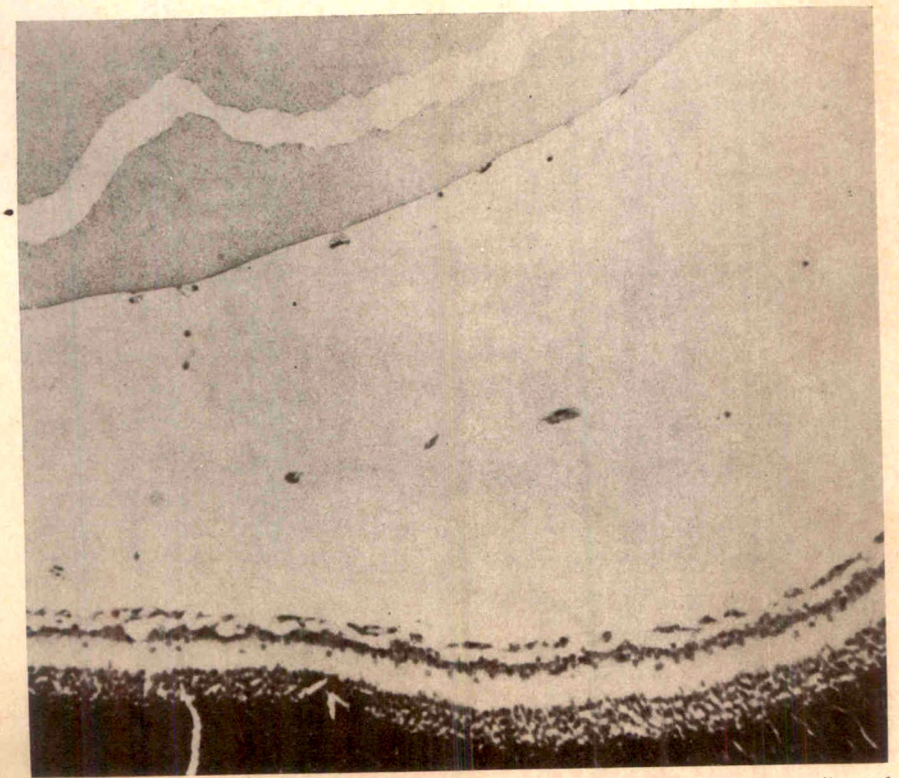


Fig. 6 (Edwards and associates). Hyaloid vessels in young rat (hematoxylin and eosin, ×80).

observed for the development of cataracts. Eighty-four percent of the rats receiving this drug before the age of 10 days developed lens opacities. Bleomycin given to 10-day-old rats or older did not induce cataract formation. The cataracts initially occurred in the nuclear area and later involved most of the lens whether or not bleomycin was later discontinued. The presence of the tunica vasculosa lentis in rats younger than 10 days old may explain why cataracts developed only in these young animals.

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Ophthalmic Miniature

aspirin, n. (pharm.)—A hybrid coined by H. Dreser in Pflüger's Archiv in 1899. The acetylosalicylic acid occurs in the flowers of the plant *Spiraea ulmaria*. In order to distinguish from this natural product the same substance gained chemically, the word aspirin was formed by Dreser from priv. pref. a-, the above mentioned plant *Spiraea*, and chem. suff. -in. Hence aspirin prop. means "acetylo-salicylic acid which is gained not from the *Spiraea ulmaria* (but in a chemical way)."

Klein, *Etymological Dictionary of the English Language*

NOTES, CASES, INSTRUMENTS

THE EFFECT OF ASPIRIN ON REBLEEDING IN TRAUMATIC HYPHEMA

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Aspirin has often been used as an oral analgesic in the management of pain associated with traumatic hyphema. However, aspirin has an inhibitory effect on the blood clotting mechanism by its action on platelets, so it would be contraindicated in a disease process depending on clot formation for resolution. Newell[1] warned about the prolonged bleeding time following ingestion of aspirin and suggested that we forego its use in patients who were to have intraocular surgery. Stuart's[2] studies showed that aspirin inhibited collagen-induced platelet aggregation in doses of 300 mg or more per day. This effect began as early as 15 minutes after the first dose of aspirin. Rebleeding is a serious hazard in traumatic hyphema. Secondary hemorrhages frequently occur after total or partial clearing of the initial hyphema. The reason for rebleeding is not known but it is possible that the clot in the initially torn vessel is lysed before permanent closure occurs. If platelet aggregation is diminished by aspirin, a new plug is not formed and the bleeding continues to fill the anterior chamber. Smith and Christensen[3] showed that systemic administration of aspirin in therapeutic doses substantially reduced fibrinolytic activity in the aqueous of the rabbit. There is no evidence that this occurs in humans. If it does, however, there is a balance between the platelet system and the fibrinolytic system and aspirin has a much greater effect on the platelet system.

To decide whether aspirin administration increased the chance of rebleeding, we undertook a retrospective study of patients treated with aspirin and those treated without.

MATERIAL AND METHODS

The charts of 127 patients with traumatic hyphema admitted to the Hospital for Sick Children from Jan. 1, 1970, to Dec. 31, 1973, inclusive, were reviewed. From March 1, 1974, to Feb. 28, 1975, the use of aspirin was forbidden for patients admitted with hyphema and a further 28 patients were studied, two of whom received aspirin before admission. The degree of hyphema was stated as Grade 1, if bleeding was microscopic or filled less than one third of the anterior chamber; Grade 2, if bleeding filled one third to one half of the anterior chamber; and Grade 3, if bleeding filled more than half the anterior chamber. Patients in each grade were assigned to one of four groups: those who had received aspirin and those who had not, and those in whom rebleeding occurred and those in whom it did not. The groups were then compared and the results analyzed by χ^2, Fischer, and Tocher statistical techniques.

RESULTS

The results of these analyses for the retrospective part of the study are shown in Table 1. The incidence of rebleeding in patients with Grade 1 hyphema was significantly increased by the administration of aspirin. The number of patients in each group with Grades 2 and 3 hyphema was too small to allow satisfactory testing by χ^2. Therefore, Fischer and Tocher analyses were performed for Grades 2 and 3 hyphema. The differences were not significant. Results for the prospective part of the study are shown in Table 2. Since the use of aspirin has been forbidden in patients admitted with hyphema, the trend is toward fewer

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Presented at the American Ophthalmological Society Meeting, Hot Springs, Virginia, May 30, 1975.

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TABLE 1

ASPIRATION ADMINISTRATION AND THE INCIDENCE OF REBLEEDING IN TRAUMATIC HYPHEMA: RETROSPECTIVE STUDY

Grade	No. With Aspirin	No. Without Aspirin
1		
Rebleed	7*	4*
No rebleed	10	67
Total	17	71
2		
Rebleed	2	0
No rebleed	6	19
Total	8	19
3		
Rebleed	3	0
No rebleed	3	6
Total	6	6

* Rebleeds with aspirin in Grade 1, 41%; rebleeds without aspirin, 6%. Significant to $P \leq .01$. Total rebleeds with aspirin in Grades 1–3, 39%; total rebleeds without aspirin in Grades 1–3, 4%.

rebleeds; however, as this is only for a 12-month period, the numbers are too small to be statistically significant.

DISCUSSION

Apparently aspirin administration tends to increase the incidence of rebleeding in traumatic hyphema. In the natural history of a hyphema the platelets aggregate to form plugs in the ends of the ruptured blood vessels. A clot then forms and eventually retracts and absorbs. Aspirin inhibits platelet aggregation and thus interferes with clotting.[4–10] Platelets adhere to one another in the presence of adenosine diphosphate. The initial aggregation is reversible, but later it becomes irreversible because endogenous adenosine diphosphate is released from the platelets themselves. Aspirin inhibits the release of endogenous adenosine diphosphate preventing platelet aggregation and plug formation, thus prolonging the bleeding time.[4,5–7] As little as five grains of aspirin can produce this defect, which persists for as long as four to seven days after salicylate has been cleared from the blood, a period corresponding to the life span of the platelet.[6,7]

In patients with traumatic hyphema where the previous history of aspirin ingestion is uncertain, platelet aggregation and bleeding time should be checked, and if diminished, a platelet transfusion may be considered. Salicylate levels in the blood are only detected if the patient is on large doses of aspirin. One five-grain tablet would barely give a detectable level. Because rebleeding in hyphema carries a serious risk of permanent damage to the eye, aspirin should not be used as an analgesic. The analgesics, acetaminophen (Tempra, Tylenol), codeine, and meperidine HCl (Demerol), and the tranquilizer diazepam (Valium), are suitable drugs for this condition.

SUMMARY

Often used as an oral analgesic in the management of pain associated with traumatic hyphema, aspirin has an inhibitory effect on the blood clotting mechanism by its action on platelets. We carried out a retrospective study of patients with traumatic hyphema treated with aspirin and showed

TABLE 2

ASPIRIN ADMINISTRATION AND THE INCIDENCE OF REBLEEDING IN TRAUMATIC HYPHEMA: PROSPECTIVE STUDY

Grade*	No. With Aspirin†	No. Without Aspirin†
1		
Rebleed	0	1
No rebleed	0	13
Total	0	14
2		
Rebleed	0	0
No rebleed	0	4
Total	0	4
3		
Rebleed	2	2
No rebleed	0	6
Total	2	8

* Total rebleeds in Grade 1 = 7%.

† Total rebleeds with aspirin in Grades 1–3, 100% (patients received aspirin before admission); total rebleeds without aspirin in Grades 1–3, 11.5%.

that the incidence of rebleeding significantly increased with aspirin administration.

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A LABORATORY ANIMAL MODEL FOR PHACOEMULSIFICATION PRACTICE

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Phacoemulsification of cataracts through a small corneal incision with an ultrasonic needle or a miniature mechanical cutter has aroused considerable interest in recent years.[1-8] In the course of testing a miniature turbine-driven phacofragmentator designed for fragmenting hard nuclear cataracts, we developed a model that simulates a living eye with a cataract and can be used as a practice eye for testing of such instruments and acquiring skill in their use.

Material and methods

This model consisted of a human cataract removed in its capsule and implanted in the anterior or posterior aqueous chamber of a rabbit eye.

The rabbit was anesthetized with sodium pentobarbital (24 mg/kg of body weight) given intravenously. The pupil of the eye chosen for implantation was maximally dilated with 2% atropine drops and 2% cyclopentate drops.

An eyelid speculum was used to retract the eyelids and a superior rectus bridle suture was placed for traction and fixation. A corneal incision was made with a keratome at 12 o'clock and was enlarged to 10 o'clock and 2 o'clock with corneal scissors.

The anterior capsule of the crystalline lens was grasped and removed with an extracapsular forceps and the lens cortex and nucleus removed with a lens spoon, leaving the posterior capsule intact. Then the human cataract specimen, obtained from a hospital operating room and refrigerated in sterile saline before use, was placed in a lens loop and inserted either in the posterior or anterior aqueous chamber while the corneal flap was raised with fine forceps (Figure, top). After the cataract was positioned in the central portion of the selected chamber, the corneal incision was closed with a continuous interlocking 8-0 silk suture, leaving a 2- or 3-mm opening for insertion of a phacoemulsification instrument (Figure, bottom).

When this model is used with a phaco-

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This study was supported by National Aeronautics and Space Administration research grant NSG 3021 and Public Health Service research grant EY-00227 from the National Eye Institute, National Institutes of Health.

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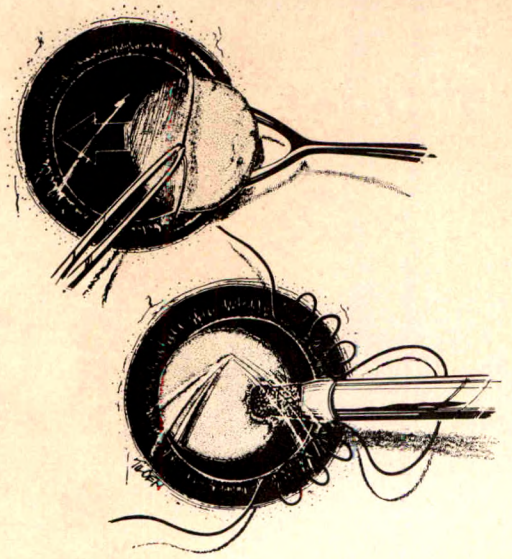


Figure (Tolentino and Liu). Top, Hard nuclear cataract placed in a wire loop was inserted into the anterior chamber of an animal eye. Bottom, Corneal incision was closed with a continuous interlocking 8-0 silk suture, leaving a 2- or 3-mm opening for insertion of instrument tip.

emulsification instrument that infuses and aspirates, the sutures must be pulled tight to minimize leakage of fluid from the anterior chamber. When it is used with an instrument that infuses but does not aspirate,[4] the sutures should be tied loosely to allow irrigation of lens material through the corneal opening.

Discussion

An increasing interest in phacoemulsification stresses the need for a laboratory animal that can be used for practicing the technique. Moreover, improvement of phacoemulsification instruments and techniques requires the use of an animal model that simulates conditions in the human eye. Although some domestic animals may develop a naturally occurring cataract, they are not always available. Also, a traumatic cataract in a laboratory animal is unsatisfactory because it is soft and does not resemble a human senile cataract, which often has a hard nucleus. Therefore, such models cannot be used to gauge the fragmentation or cutting efficiency of an instrument.

Our laboratory model is easy to produce and can be used either for practice surgery or for evaluation of an instrument designed to remove a cataract through a small incision. The ready availability of rabbits, whose eyes have large anterior segments, and of human cataract specimens provides surgeons with the elements of a practical animal model simulating a clinical case of human senile cataract.

We have used replications of this model more than 100 times to test cutting effectiveness and other functions of several phacoemulsification and fragmentation instruments. The model has been especially helpful in evaluating the infusion and suction system of the cataract instruments because of the way it simulates the conditions during phacoemulsification or phacofragmentation.

Summary

A human cataract, removed in its capsule, and implanted in either the anterior or posterior aqueous chamber of a rabbit eye, provided a model system that simulated a clinical case of human senile cataract. Such a model can be used for practice surgery or for evaluation of an instrument designed to remove a cataract through a small incision.

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SPECTACLE AID FOR CONTACT LENS WEARERS WITH BILATERAL APHAKIA

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Patients with bilateral aphakia are often candidates for contact lens optical correction, but these patients may be handicapped by their aphakia in accomplishing contact lens insertion.

We developed a spectacle to help these patients insert a contact lens. Two spectacle lenses are independently hinged to the spectacle frame so that each can be flipped up out of the optic axis (Fig. 1). One lens is an aphakic near correction (+14.00 diopter sphere) and the other lens is a phakic near correction (+3.00 diopter sphere) (Fig. 2). The patient wears the spectacles with the +14.00 diopter lens down and the +3.00 diopter lens up to insert the first contact lens; he then flips up the +14.00 diopter lens and flips down the +3.00 diopter lens over the contact lens to insert the second contact lens. The spectacles are then removed.

A series of patients with bilateral aphakia found these spectacles helpful in manipulating their contact lenses, especially in the initial phases of contact lens handling and wear. Some patients ultimately found they were able to abandon the +3.00 diopter lens and no longer needed it when inserting the second contact lens.

This device can greatly aid aphakic contact lens wearers, especially those with bilateral aphakia who have not previously worn contact lenses.

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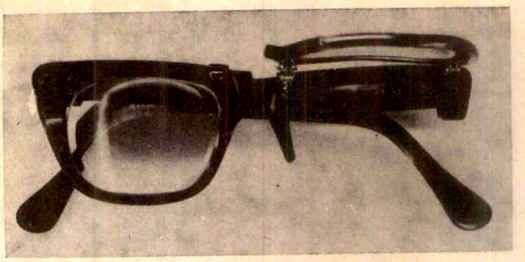


Fig. 1 (Brown, Kramer, and Erickson). Spectacle lenses are independently hinged to spectacle frame.

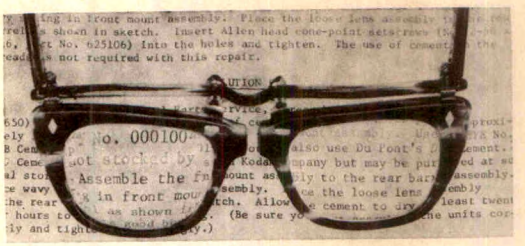


Fig. 2 (Brown, Kramer, and Erickson). The right lens is an aphakic near correction (+14.00 diopter sphere) and the left lens a phakic near correction (+3.00 diopter sphere).

SUMMARY

A spectacle aid has been developed for helping patients with bilateral aphakia insert contact lenses.

ACKNOWLEDGMENT

The spectacle aid was manufactured by Jenkel-Davidson, House of Vision Optical Company, 816 Mission St., San Francisco, CA 94103, and is available upon request.

A NEW PORTABLE APPLANATION TONOMETER

MICHAEL E. YABLONSKI, M.D.
Minneapolis, Minnesota

By attaching the standard Goldmann plastic applanation doubling prism to the stylus of a Scherr Tumico dynamometer,

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Reprint requests to Michael E. Yablonski, M.D., Department of Ophthalmology, University of Minnesota, A-684 Mayo Memorial Bldg., Minneapolis, MN 55455.

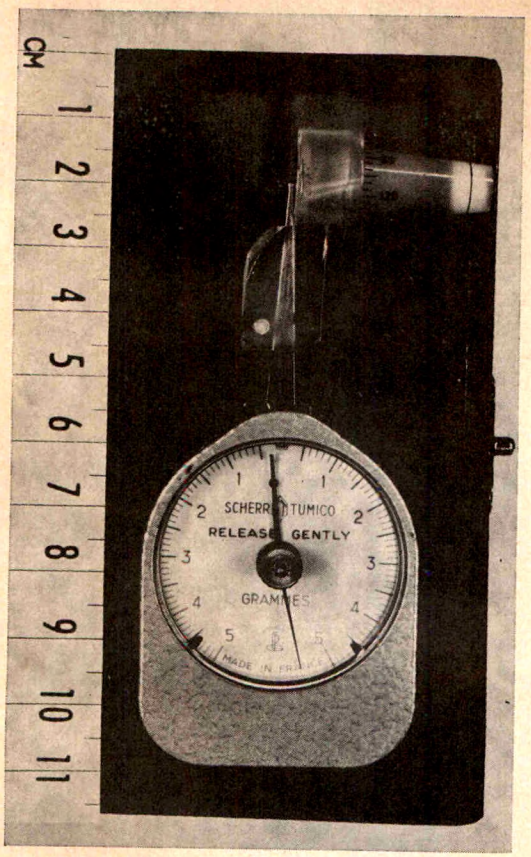


Fig. 1 (Yablonski). Basic portable applanation tonometer.

I constructed a portable applanation tonometer that is accurate and easy to use. The basic device (Fig. 1) is 10 cm long, lightweight, and easy to handle.

The results obtained with this portable tonometer (Fig. 2) are not appreciably different from those obtained with the standard slit-lamp mounted Goldmann applanation tonometer. The points (Fig. 2) were obtained from 100 consecutive eyes. Thirty-three of the points were determined on a double-blind basis. I knew the initial results of the remaining points at the time of the second determination. The results of the two different methods of comparison were not significantly different.

The device is easy to use. Fluorescein is instilled in the eye and a blue light illuminates while the tonometer probe is applied to the cornea. The end point is the same as with the standard Goldmann tonometer. This end point was seen with the unaided eye and magnification was unnecessary.

The force in grams required to produce the end point is shown on the dial scale of the dynamometer. This force multiplied by a factor of 10 gives the applanation pressure in millimeters of mercury. Because the dial scale is positioned on the side of the instrument, it cannot be read directly by the examiner. An assistant may read the dial while the examiner observes the end point. However, the need for an assistant was eliminated by modifying the device (Fig. 3). A mirror was placed at a 45-degree angle to the dial surface to enable the examiner to view the dial. Also, the second hand of the dial is pushed by the first hand and registers the highest force exerted during the procedure. By carefully increasing the force and stopping as soon as the applanation end point is reached, one may then determine this force afterward from the second hand. Most of the points (Fig. 2) were determined by this method. The disadvantage of this method is that one cannot exceed the end point and then decrease the force until the end point

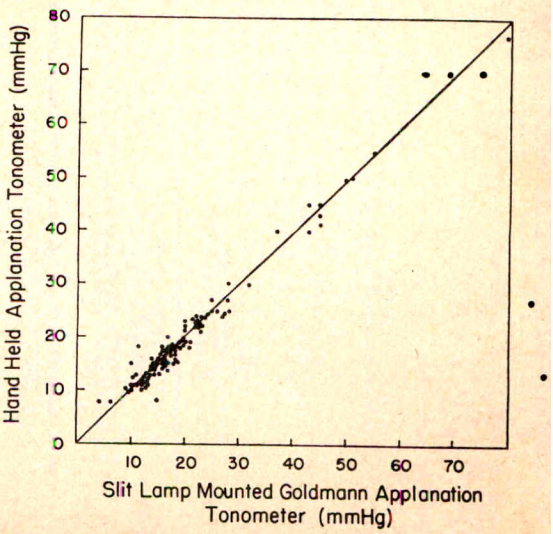


Fig. 2 (Yablonski). Comparison between measurements with portable applanation tonometer and slit-lamp mounted Goldmann applanation tonometer.

is reached. Nevertheless, with a little practice one can learn to stop as soon as the end point is reached, producing accurate and reproducible results. There is an attached disposable blue penlight (Fig. 3) that is most convenient, although any good source of blue light will suffice.

This device has many advantages over other portable applanation tonometers. It is small and portable. The end point is easily determined and familiar to most ophthalmologists. The device is relatively inexpensive. The dynamometer retails at $30 and any standard Goldmann applanation doubling prism may be used. Therefore, the total cost is less than $125, including construction.

Furthermore, this tonometer can be used with the patient in any position. The patient may sit up, lie supine, or assume some midway position. The examiner must subtract the dial reading obtained at the end point from that obtained before application of the force. I find it convenient to have the patient supine. If he is looking straight up, the applanation probe is placed vertically and the dial reads 4.5 g before application of the force, due to the weight of the Goldmann applanation probe and its mounting. If the applanation pressure is 20 mm Hg, the dial will read 2.5 g at the end point. However, though the patient is supine he may not prefer to look straight up and then I tilt the device appropriately to apply the tonometer flush with the cornea. This is convenient. The device is easiest to hold laterally to the eye by resting one's fingers against the zygomatic arch to steady things. The other hand may be used to help the patient hold the eyelids open.

This device is valuable when ophthalmologists cannot conveniently use the slit lamp, for example, in the operating room, on bedridden patients, and the like.

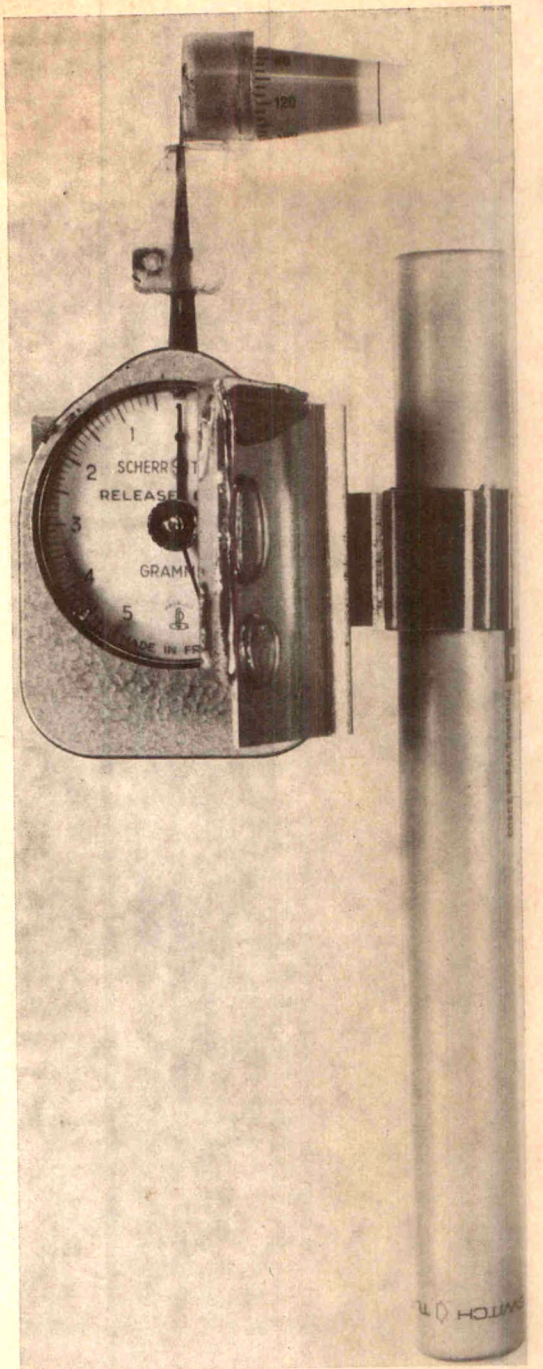


Fig. 3 (Yablonski). Modified portable applanation tonometer with attached blue penlight and mirror.

Summary

A portable applanation tonometer consisted of a Goldmann applanation doubling prism mounted on a dynamometer. Results obtained on 100 consecutive eyes showed a good correlation with the standard slit-lamp mounted applanation tonometer. This porta-

ble tonometer is small and easy to use, utilizing the same end point as the standard Goldmann tonometer. In addition, the patient may assume almost any position.

NICTITATING MEMBRANE IN TRISOMY 18 SYNDROME

José M. García-Castro, M.D., and Luz Carlota Reyes de Torres, M.S.
San Juan, Puerto Rico

The ocular malformations usually associated with trisomy 18 syndrome are microphthalmia, colobomata, and corneal opacities.[1,2] Lautridou and associates[3] confirmed the occurrence of these anomalies and demonstrated other malformations histopathologically, including an irregular thickness of the cornea, disappearance of Bowman's membrane, peripheral anterior synechiae, coloboma of the retina, and small folds of the internal layer of the retina at the level of the macula and the ora serrata, without abnormalities of retinal maturation.

We observed a nictitating membrane with trisomy 18 syndrome. To our knowledge this is the first instance that such an abnormality has occurred in this syndrome.

Case report

This boy, the fourth child of a 24-year-old woman, was born after 43 weeks' gestation. Birth weight was 2,290 g; crown-heel and crown-rump measurements were 44.5 and 31.0 cm, respectively; the circumference of the head was 35.5 cm; the chest, 28.0 cm; and the abdomen, 25.0 cm. Pertinent clinical findings included a prominent occiput; characteristic facies; microphthalmia; nictitating membrane bilaterally; low-set ears, posteriorly rotated and with immature pinnae; micrognathia and a small mouth; short, webbed neck with cervical ribs demonstrated on roentgenographic examination; short sternum and small nipples; clenched hands with the characteristic overlapping of fingers; rocker-bottom feet; and hypoplastic finger and toe nails (Figure). Dermatoglyphic study revealed arches on all ten fingers, distal axial triradii, and a complete simian crease on the right palm and a bifid one on the left. Though no heart murmurs were heard on physical examination, atrial and ventricular septal defects were discovered on pathologic examination. Using regular staining techniques, cytogenetic evaluation revealed a chromosome complement of 47, XY, +18.

Discussion

This patient had the classic clinical and dermatoglyphic findings of trisomy 18 or Edwards syndrome, established cytogenetically. Moreover, the infant presented with a bilateral nictitating membrane (Figure). This membrane, in contrast with those of lower species, was horizontally placed and moved cephalad for closure. At times, the membrane would cover the conjunctiva and the cornea completely, giving the impression of cloudiness. Because of this, and also because of the microphthalmia and puffiness of the eyelids, our initial impression was that of corneal clouding, a finding associated with trisomy 18 syndrome.[1,2] Thus, in patients with trisomy 18 syndrome presenting with cloudy corneas, a careful search may reveal nictitating membranes. Postmortem evaluation of the eye was denied.

Summary

A 2,290-g infant boy born after a 43-week gestation had the classic, somatic, and dermatoglyphic findings of trisomy 18 (Edwards) syndrome. The diagnosis was established cytogenetically. A bilateral nictitating membrane was present. In contrast to those in lower species this membrane was established horizontally and moved cephalad for closure. Thus, the membrane occasionally covered the conjunctiva and cornea completely, giving the impression of corneal clouding. Postmortem studies were not permitted.

From the Regional Medical Program of Hereditary Diseases, Department of Pediatrics, and Medical Genetics Laboratory, Clinical Research Center, School of Medicine, University of Puerto Rico. This study was supported in part by grants 74-203-83-56 of the Regional Medical Program and RR 0063-12 of the General Clinical Research Center, National Institutes of Health.

Reprint requests to José M. García-Castro, M.D., Programa Médico Regional de Enfermedades Hereditarias, G.P.O. Apt. 1764, San Juan, PR 00936.

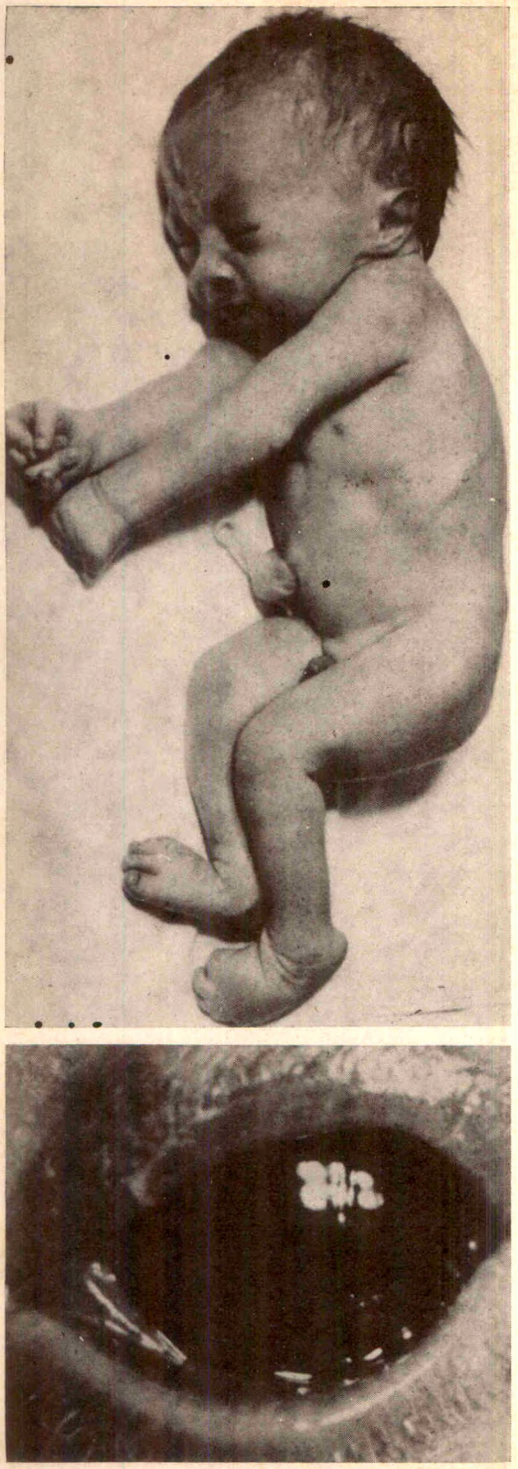


Figure (García-Castro and Reyes de Torres). Top, The characteristic features of trisomy 18 syndrome. Bottom, The nictitating membrane is positioned horizontally across the eye. Microphthalmia is also evident.

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CORNEAL HOLDER

Thomas E. Slappey, B.S.

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Much improvement has been made recently in the preservation of human corneal tissue used in penetrating keratoplasty.[1] The M-K (McCarey-Kaufman) medium, a tissue culture solution developed by McCarey and Kaufman, has successfully maintained viable human corneas for one week. As this medium and other methods preserve corneas in a viable state, there must be an occasion when excess or other preserved corneas are stored beyond their useful storage time limits. In this event, these corneas can be converted to one of the long-term lamellar preservation systems.[2]

To facilitate the use of these corneas, I developed a corneal holder* (Figure). Although other holders for different purposes have been developed, I have not found these satisfactory since they require the presence of an assistant, and are somewhat clumsy to work with.

Corneas stored in M-K media, and a few other preservation systems, are excised with a 2- to 3-mm rim of sclera. The corneal

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* This instrument is available through Syber Inc., 2616 S.W. 14th Dr., Gainesville, FL 32608.

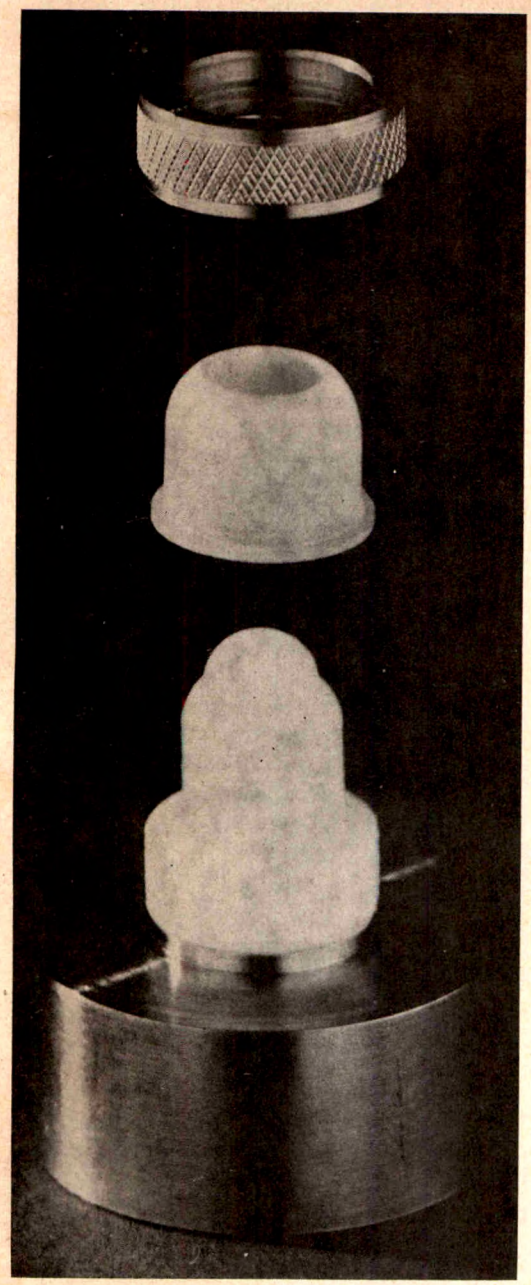


Figure (Slappey). Corneal holder featuring a pedestal, retaining ring, and scleral sealing sleeve.

holder allows the surgeon to place the excised cornea in a holding device that allows dissection of a lamellar graft of any size.

The corneal holder consists of a heavy metal base with a protruding cutting pedestal. The base of the pedestal is threaded to accept a retaining ring. A scleral sealing sleeve is used to lock the scleral rim of the cornea to the cutting pedestal. The retaining ring is then tightened, thus locking the sleeve to the cutting pedestal.

The apex of the cutting pedestal is designed to trap air under the cornea while the retaining ring locks the sealing sleeve, creating an air cushion. The air cushion allows the flattening of the cornea during lateral lamellar dissection.

The corneal holder is economically manufactured, simple to use, and easily sterilized. It is especially well adapted to use by surgeons who do not always have an assistant in the operating theater. The moderately heavy construction allows the surgeon to use both hands for the lamellar dissection.

Summary

As a result of the widespread use of M-K (McCarey-Kaufman) medium preserved corneas, as well as other methods of preserving corneas in a viable state, I developed a corneal holder to facilitate the lamellar dissection of previously excised whole human corneas. Consisting of a moderately heavy base, cutting pedestal, scleral rim-sealing sleeve, and retaining ring, the corneal holder is economically manufactured, simple to use, and easily sterilized. Its weight and construction allow unassisted dissection of a lamellar graft of any size.

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TREATMENT OF BAND KERATOPATHY

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AND
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Memphis, Tennessee

Band keratopathy is usually secondary to chronic eye disease such as uveitis or absolute glaucoma. Pain and photophobia, the usual presenting symptoms, are caused by erosion of the epithelium overlying the calcium. Currently edetic acid (EDTA) chelation is the most widely accepted treatment.[1,2] Sisson[3] in 1934 advocated chipping off the calcium opacities under topical cocaine anesthesia. We reintroduced the simple procedure of superficial keratectomy for removing band keratopathy from the calcium deposition in the cornea in patients who have either pain or decreased vision, according to H. E. Kaufman (personal communication, 1969).

The technique is as follows: Topical anesthesia is administered and the eye is held open with an eyelid speculum. An operating microscope is used. The globe is fixated with toothed forceps and the epithelium removed from the cornea with a No. 15 scalpel blade. As the epithelium is removed, the surgeon will notice a gritty sensation produced by the calcium in Bowman's membrane. The scalpel is scraped vigorously across the cornea much like sharpening a razor on a leather strop. As the scraping is done, small flecks of calcium will begin to break from Bowman's membrane. This is continued until all visible calcium is removed from the surface of the cornea. When the calcium has been removed from the superficial cornea, the gritty sensation disappears. After the calcium removal, the eye is patched for approximately one week to allow the epithelium to heal.

Fourteen eyes in 12 patients have been treated in this manner. In the eyes that were blind and painful, the symptoms were relieved after the calcium was removed from Bowman's membrane. In patients with healthy eyes, except for the band keratopathy, the pain was relieved and vision improved. Two complications occurred in this series. One patient with rubeosis irides developed a hyphema that resolved spontaneously. A second patient developed recurrent erosion for several days after the procedure.

A superficial keratectomy originally described in 1934 has been made even easier with the use of the microscope. There is no need for special medication, and the conjunctival irritation or epithelial breakdown that EDTA treatment may produce usually does not occur.

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Reprint requests to Thomas O. Wood, M.D., Department of Ophthalmology, University of Tennessee Center for the Health Sciences, 858 Madison Ave., Memphis, TN 38163.

SUMMARY

Band keratopathy, caused by a variety of chronic ocular or systemic diseases, produces pain, photophobia, and decreased vision. A simple method for treating band keratopathy consists of scraping the cornea vigorously with a No. 15 scalpel blade until the superficial calcium has been removed.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

AMERICAN OPHTHALMOLOGICAL SOCIETY

The 111th annual meeting of the American Ophthalmological Society took place at The Homestead, May 29-31, 1975. M. Elliott Randolph presided. This meeting of our nation's oldest medical specialty group has been the progenitor of clinical ophthalmic meetings in North America. The 20 papers, well presented by fellows and invited guests, showed greater incorporation of electron microscopy and biochemical analysis than in many previous meetings.

Studies summarized in these presentations frequently trace continuity to presentations by the same author or other fellows decades ago. Autobiographical experiences often charmingly clinch clinical data, and the program was opened in this vein by R. P. Burns and M. H. Potter from the University of Oregon. Dr. Burns reported an apparent resurrection of adenovirus type 19 causing epidemic keratoconjunctivitis and acknowledged that he was the hapless third patient in the reported series. Incubation was apparently five days or less. The conjunctivitis appeared hemorrhagic and pseudomembranous. Bilateral uveitis may also occur with adenovirus 19.

D. Guerry III, H. Wiesinger, and J. Harbison reported a unique spontaneous bilateral proptosis with secondary glaucoma subsequent to spontaneous dural arteriovenous fistula. Surgical therapy with transcranial orbital decompression improved visual acuity from light perception bilaterally to 20/30 and 20/40.

A new eponym, Walshian eye movement, was introduced by A. Jampolsky for those extraocular rotations that are separately known and true. An unusual range of perhaps "perversion movements" was demonstrated in a motion picture showing extreme voluntary control in some patients. F. P. Calhoun, Jr., reported on painless and relentless glaucoma of mid-life in the patient with congenitally small or extremely hyperopic eyes. High pulse pressures were noted on tonography. Surgical intervention was followed by a high incidence of complications in the author's six cases.

L. A. Lloyd reported a large series of hypertelorism in 63 patients with extensive cosmetic deformities. Orbital translocation repairs requiring ten or 12 hours on the operating table should also be paralleled by critical genetic counseling to the families. Correction requires an enduring team of plastic surgeons, neurosurgeons, radiologists, dentists, psychiatrists, and ophthalmologists.

Central areolar pigment epithelial dystrophy over three generations was reported by J. G. Dobbie, C. L. Fetkenhour, and D. Shoch. Sudden, severe visual loss was often precipitated by macular hemorrhage.

The usually severe metabolic defect of hyperornithinemia was reported by C. McCulloch and E. B. Marliss in a young male with gyrate choroidal atrophy. Elevations of glucose levels produced drops in blood ornathine levels and indicated an interrelationship of glucose metabolism to this amino acid. Hereditary patterns are not clear.

F. W. Newell reported a 20-year pursuit of diagnosis in a heritable form of mucolipidosis. There was corneal clouding since infancy with mental and physical retardation. The electroretinogram was extinguished. This was identified as an enzyme deficiency in the lysosomes with storage of mucolipids.

R. B. Welch capsuled over 700 reports on metallic intraocular foreign bodies, and documented photographically the reversal of siderosis bulbi following removal of a ferrous foreign body. A second patient showed spontaneous extrusion of intraocular copper.

C. Kupfer and M. K. Kupfer reported the rare clinical finding of bilateral essential iris atrophy. Histology indicated that pathogenesis was nonvascular.

Using 127 patients with demonstrated increased tendency to rebleeding when aspirin was administered, J. S. Crawford analyzed unknowns in contusion hyphema.

R. K. Forster and E. W. D. Norton summarized 50 cases of endophthalmitis verified by intraocular culture. Utilization of intraocular antibiotics in carefully calculated small dosages may avoid retinal toxicity and bring control if properly and promptly administered. In a postmortem verification, there was histopathologic documentation of chronic cystoid macular edema following cataract extraction. The presence of a lamellar macular hole negates the otherwise generally encouraging visual prognosis.

S. D. McPherson and H. T. Tucker emphasized posterior form sympathetic ophthalmia in two illustrative cases without any anterior uveal involvement. The tragic seriousness of this disease was underscored.

Photocoagulation was reported by R. J. Brockhurst as improving the prognosis of posterior polar retinal detachment associated with congenital optic pits.

J. C. Calhoun and R. D. Harley extended the experience of Douvas with the roto-extractor for anterior segment surgery in children. Complications were few. New details of recurrent granular corneal dystrophy were identified by M. M. Rodrigues in a 36-year-old white man having bilaterial penetrating keratoplasties 15 years previously.

A. G. DeVoe presented the Sixth Verhoeff Lecture. He summarized current fluctuations in cataract surgery and advised hospitalization as a safeguard in the presence of complications and to facilitate knowledgeable peer overview. He urged critical analysis in the two currently controversial steps of phacoemulsification and phacoprosthesis. Greater strides in success of cataract extraction were underscored by improvements in suturing and microsurgical guidance.

Discussion throughout the meeting was enlarged by visitors and foreign guests.

The 113th annual meeting will take place in Kilauea, Hawaii, May 14-16, 1976.

ARTHUR H. KEENEY

EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY

The European Ophthalmic Pathology Society held its 14th Annual Meeting in Oslo, Norway, June 3-6, 1975. J. A. C. Wadsworth, Durham, North Carolina, was the honored guest. Eight European guests and 32 members attended the meeting, which was perfectly organized by Professor and Mrs. K. Arnesen. The scientific sessions were held at the University of Oslo, Institute of Preclinical Odontology. A reception was given at the city hall by the mayor of Oslo and the annual dinner took place at Restaurant "Najaden," Bygdøy, where the famous Viking Ship House and Kon-Tiki House were also visited. S. Ry Andersen, Denmark, was elected president and O. A. Jensen, Denmark, corresponding secretary. A. A. Henriquez, of Spain, and D. Toussaint, of Belgium, were elected new members. The next meeting will be a joint meeting with the Verhoeff Society in Washington, L. E. Zimmerman being the organizing secretary.

The 32 members attending the meeting were: S. Ry Andersen (Denmark); K. Arnesen (Norway); N. Ashton (Great Britain); J. Babel (Switzerland); R. Barry (Great Britain); M. Brihaye van Geertruyden (Belgium); J. Böck (Austria); A. Brini (France); J. G. Cunha-Vaz (Portugal); B. Daicker (Switzerland); P. Danis (Belgium); P. Dhermy (France); P. C. Donders (Netherlands); F. Fanta (Austria); A. Garner (Great Britain); A. Hamburg (Netherlands); M. Hanssens (Belgium); O. A. Jensen (Denmark); E. Kock (Sweden); E. Landolt (Switzerland); W. R. Lee (Great Britain); O. Litricin (Jugoslavia); O-E. Lund (West Germany); W. A. Manschot (Netherlands); G. Morgan (Great Britain); J. Mullaney (Ireland); G. Naumann (West Germany); A. Nover (West Germany); M. Quintana (Spain); R. Seitz (West Germany); A Tarkkanen (Finland); and M. Vogel (West Germany).

P. Bec (France) was unable to attend.

Guests were: E. Balestrazzi (Italy); G. Goder (East Germany); A. Henriquez (Spain); E. Hinzpeter (West Germany); L. Merenmies (Finland); H. Slezak (Austria); F. Stefani (West Germany); and D. Toussaint (Belgium). O. A. JENSEN

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VISION RESEARCH PROGRAM PLANNING

For the people of this nation, confronted with the steadily increasing prevalence of vision impairment and blindness, preservation and restoration of vision require coordinated programs of research, education, and patient care. These interrelated programs must provide for research and research training in the basic and clinical sciences pertaining to vision, education in the fundamental biological and applied clinical sciences related to the eyes and associated structures, and health care for patients with vision disorders and eye disease. To provide essential new knowledge for the alleviation of eye disease, the research program must be extensive, multifaceted, sustained, and adequately supported.

The National Eye Institute, established in 1968, is the principal national resource for research related to the prevention, diagnosis, and treatment of eye disease. Recognizing this, the National Advisory Eye Council—a body of 12 citizens appointed by the Secretary of Health, Education and Welfare to render advice regarding activities of the National Eye Institute—established a Vision Research Program Planning Committee. This committee was charged with analyzing current research related to the eyes and vision throughout the United States and formulating recommendations for the future development and financing of vision research.

With the participation of 25 consultants representing the major aspects of vision research, aid from the National Eye Institute staff and endorsement of the National Advisory Eye Council, this committee has produced a Report on Vision Research Program Planning, which may be obtained from the National Eye Institute, Bethesda, Maryland 20014.

Volume 1 of this report begins with an introductory statement by Carl Kupfer, director of the National Eye Institute. General information on vision research and vision research program planning is then presented, followed by data on vision re-

search support in the United States and on the research program of the National Eye Institute. Specific features of ongoing research, statements concerning the major scientific needs and opportunities in each National Eye Institute research program, material on vision research training, and summary research program data comprise the main body of the text. Volume 1 concludes with the committee recommendations for coordinating and strengthening the national program of vision research.

Volume 2 of this report contains a detailed analysis of the five National Eye Institute research programs: Retinal and choroidal diseases, Corneal diseases, Cataract, Glaucoma, and Sensory and motor disorders of vision, as well as a detailed appraisal of Vision research training. For each program a statistical summary, narrative evaluation, and assessment of major research needs and opportunities are presented. This comprehensive review constitutes the foundation for the summary information incorporated in volume 1.

Of particular importance are the committee recommendations for the future development of the national vision research program. These recommendations provide for the following: (1) periodic evaluation of the National Eye Institute research program; (2) establishment by the research scientists of the major research needs and opportunities; (3) dissemination of National Eye Institute research program planning information to the nation's scientists and all other interested parties; (4) enhanced communication among research scientists in related fields of investigation; (5) enhanced communication with representatives of the Federal Government, the scientific community and the general public; (6) development of special types of research grants to encourage clinical research and other forms of investigation that warrant stimulation; (7) development of special types of research training programs to provide an adequate number of fully trained scientists in all areas of investigation; (8) selective utilization of the research contract; (9) application of the National Eye Institute intramural research program in an optimum manner; (10) assembly of biometrical and epidemiological information regarding vision disorders of blindness; (11) augmentation of special programs of public information regarding vision disorders; (12) demonstration projects related to establishing the efficacy of treatment and fostering other research related to the prevention, diagnosis, and treatment of eye disease; and (13) projection of long-term budget requirements for vision research.

Based on available information and critical professional assessment, committee projections of the support needed by the National Eye Institute extend from the current appropriation for fiscal year 1975 (July 1, 1974-June 30, 1975) to encompass a five-year period (Table).

TABLE

FIVE-YEAR NATIONAL EYE INSTITUTE APPROPRIATION NEEDS

Fiscal Year	Amount
1975 (Current appropriation)	$ 44,133,000
1976	75,000,000
1977	97,000,000
1978	112,000,000
1979	124,000,000

To achieve humanitarian and scientific national health goals related to the prevention, diagnosis, and treatment of vision disorders and eye disease, this magnitude of fiscal support is mandatory.

MANSOUR F. ARMALY
V. EVERETT KINSEY
CARL KUPFER
ALAN M. LATIES
VERNON B. MOUNTCASTLE
BRADLEY R. STRAATSMA
National Advisory Eye Council
Vision Research Program Planning Committee

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper; with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Medical Writing

Editor:

In his excellent editorial, "Toward a better understanding of medical reports" (Am. J. Ophthalmol. 79:1054, 1975), Alfred Sommer's tongue-in-cheek remark that "an investigator can automatically demonstrate that an agent is useless by using small numbers of patients and finding 'no statistically significant difference between two groups'" contains an important lesson in clinical investigation. Absence of statistical significance in an observed difference does not necessarily mean absence of a real difference —it may merely mean that the numbers were too small to detect such a difference. For this reason confidence limits are more informative than significance tests.

For a difference to be important it needs to be both medically (or biologically) important and statistically significant. When numbers are too small they cannot produce evidence of statistical significance, and when they are large they may result in statistically significant differences that are medically unimportant. An expensive headache remedy that increases the probability of relief from 60 to 63% may not be worth the extra cost, no matter how statistically significant the difference.

Medical articles containing numerical data require careful scrutiny. As Alfred Sommer says, "If we are to avoid being misled and hope to make sense of conflicting claims, we must overcome our diffidence and learn to read these works critically."

Fred Ederer
Bethesda, Maryland

BOOK REVIEWS

Synopsis of Ophthalmology, 4th ed. By William H. Havener. St. Louis, C. V. Mosby, Co., 1975. Clothbound, 594 pages, table of contents, index, 345 black and white figures. $14.50

The fourth edition of Havener's fine basic textbook for medical students continues to emphasize ophthalmoscopy with a little less than one third of its pages devoted to this subject. The synopsis is unusually readable and diagrams and photographs are used effectively. The book should not be underestimated as it covers a large variety of afflictions of the eye. There is adequate coverage of everything from neuro-ophthalmology to surgery of the eye. The book has an excellent glossary and superb index, both of which are essential parts of a synopsis intended for students.

It may be that the ophthalmic synopsis written for medical students will be replaced by audiovisual materials in the future, but until the value of the latter are proven, the textbook remains the standard for comparison. This synopsis is a fine addition to the medical student's library and is more than adequate for his needs.

J. Terry Ernest

• • •

Helfer des Augenarztes. By Karl Velhagen. Germany, VEB Georg Thieme, 1974. Clothbound, 300 pages, table of contents, over 100 black and white figures, 21 color plates. $18.60

This is a concise and precise book for the ophthalmic assistant. The first few chapters deal with the structure and function of the eye emphasizing errors of refraction and their corrections. A few of the most important ocular diseases are mentioned and defined.

The main part of the book concerns the functions and obligations of the assistant. This is dealt with in three main chapters: (1) The assistant in the office practice. This

is an interesting basic introduction but does not cover what such assistants are expected to do in the United States, such as applanation tonometry, perimetry, or orthoptic evaluation. It does not cover any medical technological aspects such as obtaining a specimen, taking cultures, and preparing and reading slides for a bacteriologic examination. (2) The second part deals with the role of the assistant in the hospital environment or clinic. Here again the role is somewhat restricted and more the obligation of a practical nurse than of an ophthalmic nurse clinician. (3) The third chapter deals with the duties of an operating room nurse in an ophthalmic theater. This obviously has to be a basic introduction as the techniques and methodology differ greatly.

This is a useful introduction for any ophthalmic assistant—orthoptist, nurse, or technician. Some aspects are obviously obsolete for this country and most assistants will need more thorough and deeper indoctrination.

F. C. BLODI

THE OCULAR FUNDUS, 3rd ed. By Arno Nover. Translated by Frederick Blodi. Philadelphia, Lea and Febiger, 1974. Clothbound, 175 pages, table of contents, index, 42 black and white figures, 112 color plates. $19.50

In its third edition this useful book on the ocular fundus has been enhanced by the addition of 20 more colored plates, all of uniform excellence, six additional black and white illustrations, and a short chapter on the vitreous body.

The clarity of the text and the positioning of the illustrations remain the same as in the previous editions, which should add to the continued popularity of the book.

Some misspelling of names, such as "Gaucher" on page 138, or misnomers such as "sickle-shaped atrophy of choroid and retina" in describing an inferior conus, are not serious drawbacks.

To many nonophthalmologists and beginners who will be the main readers of this book, some of the most puzzling phenomena are frequently the physiologic light reflexes in the retina, not only those of the macular region but others occurring along the retinal vessels and concentric with the optic disk. A color plate showing a young fundus with these varieties of physiologic retinal reflexes would be a great aid in avoiding the false diagnosis of retinal edema, one of the most common diagnostic pitfalls. Perhaps the next edition of the book will cover such topics.

BERTHA A. KLIEN

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

AMERICAN JOURNAL OF HUMAN GENETICS

TAY-SACHS DISEASE: HIGH GENE FREQUENCY IN A NON-JEWISH POPULATION. Kelly, T. E., Chase, G. A., Kaback, M. M., Kumor, K., and McKusick, V. A. (Dept. Pediatrics, Johns Hopkins Univ. School Med., Baltimore, Md.). Am. J. Hum. Genet. 27:287, 1975.

A non-Amish "Pennsylvania Dutch" semi-isolate was found to have a high frequency of Tay-Sachs gene. This high frequency could be ascribed to founder effect and may represent, in microcosm, how this mechanism could have produced the high gene frequency among Ashkenazi Jews. (1 figure, 11 references)— Authors' abstract

ALBRECHT VON GRAEFES ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE OPHTHALMOLOGIE

THE ELECTROPHYSIOLOGICAL BEHAVIOR OF NORMAL AND GLAUCOMATOUS HUMAN EYES WITH SHORT-TERM INTRAOCULAR PRESSURE ELEVATION. (German) Bartl, G., Benedikt, O., Hiti, H., and Mandl, H. (Univ. Graz, Graz, Austria). Albrecht von Graefes Arch. Klin. Ophthalmol. 195:201, 1975.

The intraocular pressure was transiently raised in eight glaucoma patients and in eight normal adults of the same age group. The changes that occurred in the ERG were the same in the glaucomatous group and in the normal group of patients. However, the changes in the visual evoked response of glaucomatous eyes differed widely from those of normal eyes. This seems to be due to the high sensitivity to pressure of the prelaminar portion of the optic nerve. The authors feel that this might be a useful method for the objective measurement of the sensitivity of papillary vessels to raised intraocular pressure. (2 figures, 1 table, 10 references)—David Shoch

ANNALES D'OCULISTIQUE

THE ETIOLOGY OF OCULAR HEMORRHAGES IN THE NEW BORN. (French) Francois, J., and Tranos, L. (Univ. Ghent, Ghent, Belgium). Ann. Ocul. 208:185, 1975.

The incidence of retinal hemorrhages in new-borns has been reported as varying from 3 to 40%. There are certain factors that seem to increase the frequency of retinal hemorrhages and these are: primiparity, the relationship of the size of the infant's head to the pelvic outlet, the duration of the delivery, the use of a vacuum extractor and hypoxia. In addition, there is a deficiency in blood coagulation in many new-borns since apparently it takes several days for the normal blood coagulation processes to develop. (10 figures, 9 tables, 53 references)—David Shoch

THE FREQUENCY OF MACULAR EDEMA AFTER CATARACT EXTRACTION. (French) Bonnet, M., Grange, J. D., and Pingault, C. (Univ. Lyon, Lyon, France). Ann. Ocul. 208:217, 1975.

Routine fluorescein angiography was performed on 50 eyes two months after cataract extraction. Eighteen percent of these eyes showed macular edema. This edema was present in 28% of patients over 65 and was thus much less frequent in patients under this age. The macular edema also seemed to be more common after corneal incisions than after corneoscleral incisions and also more frequent with delayed rupture of the hyaloid membrane than in eyes with an intact vitreous face. (3 references)—David Shoch

ARCHIVES OF ENVIRONMENTAL HEALTH

HIGH ALTITUDE STRESS AND RETINAL HEMORRHAGE. Schumacher, G. A., and Petajan, J. H. (Dept. Neurology, Univ. Vermont College Med., Burlington, Vt.). Arch. Environ. Health 30:217, 1975.

Retinal hemorrhage occurred in 36% of 39

subjects exposed to altitudes at or above 14,200 feet. In subjects with a history of vascular headaches at sea level, there was a higher incidence of and more severe altitude headache, as well as a higher incidence of retinal hemorrhage than among those previously headache-free. In subjects without altitude headache, none had retinal hemorrhage. In subjects with altitude headache, 42% had retinal hemorrhage. A progressive rise in the incidence of retinal hemorrhage was correlated with progressively greater intensity of altitude headache.

Increased retinal blood flow, retinal vessel engorgement, increased retinal vein and prevenous capillary pressure, and possibly decreased intraocular pressure may contribute to the pathogenesis of retinal hemorrhage. (2 figures, 6 tables, 13 references)—Authors' abstract

Archives of Ophthalmology

RETINAL CHANGES IN HIMALAYAN CLIMBERS. Rennie, D., and Morrissey, J. (Presbyterian-St. Lukes Med. Center, Chicago, Ill.). Arch. Ophthalmol. 93:395, 1975.

Changes in the fundus of the eye were studied in 15 members of a mountaineering expedition to Dhaulagiri, Nepal (elevation, 8,167 meters (26,795 ft.). Retinal photographs were taken at sea level and at 5,883 meters (19,300) after each climber had descended from his highest point. Five Nepali Sherpas and an additional American climber who came to the base camp late in the climb were also studied. Vascular engorgement with tortuosity, a 24% increase in arterial diameter, and a 23% increase in venous diameter were observed. Retinal hemorrhages were seen in five American climbers (33%), but in none of the Sherpas. The high incidence is striking, but the cause is unknown. We suggest that the hypoxic vasodilatation makes retinal vessels more vulnerable to sudden rises in intravascular pressure. (5 figures, 1 table, 25 references)—Authors' abstract

Brain

ALCOHOL AND HUMAN EYE MOVEMENT. Wilkinson, I.M.S., Kime, R., and Purnell, M. (Dept. Neurology, Royal Infirmary, Cambridge, England). Brain 97:785, 1974.

With blood alcohol levels between 80 and 100 mg%, the velocity of saccadic eye movement is reduced by about 20%. Smooth pursuit movement becomes impaired at relatively low blood alcohol levels with increasing dependence on saccades to keep the eyes fixed on or near the moving target. Doll's head eye movement remains normal after alcohol. (4 figures, 5 references)—Joel G. Sacks

British Journal of Ophthalmology

EXPERIMENTAL ANALYSIS OF AMBLYOPIA AND STRABISMUS. Blakemore, C., and van Sluyters, R. C. (Physiol. Lab., Cambridge, England). Br. J. Ophthalmol. 58:176, 1974.

The experimental, neurophysiological approach to the mechanism of binocular vision in the cat has revealed a large number of phenomena that bear on amblyopia and strabismus in man. In the normal cat about 80% of the neurons in the visual cortex receive input from both eyes (in varying proportions as implied in Hubel and Wiesel's terms "dominance types"); about 20% have strictly monocular input from the ipsi- or the contra-lateral eye. Exclusion of one eye by tarsorrhaphy in kittens between three weeks and three months of age has disastrous effects on the cortical cells and on the vision of the occluded eye. Almost all cells in the visual cortex contralateral to the eye that had been occluded are now driven exclusively from the ipsilateral eye. This effect cannot be reversed by a prolonged period of binocular vision, but "crosspatching" (tarsorrhapy on the other eye) can lead to a total switchover so that all cells are now driven from the initially deprived eye. The switchover, however, takes place only if the occlusion of the second eye is done before the age of four months. A judicious choice of the timing and the duration of the crosspatching can produce an animal with about equal numbers of right-eye-driven and left-eye-driven cortical cells, but with very few binocular neurons. These animals seem to acquire reasonable visual acuity with each eye, but are presumably deficient in stereopsis.

Cortical neurons in the normal cat are also characterized by specific sensitivity, that is, optimal response, to the orientation of the target (the direction in which a black-white edge

is offered). This property of cortical cells is, apparently, acquired through appropriate visual experiences during a plastic developmental stage. This is demonstrated in experiments in which the visual experience of kittens is limited to an array of either vertical or horizontal black-white edges. The cortex of these animals ultimately contains no neurons responding optimally to lines at right angles to those of their early environment. Presumably, there is meridional amblyopia, analogous to the condition observed in humans with extremely high astigmatism, undiagnosed and therefore untreated in infancy. Keeping kittens in the dark except for regular exposure to striped patterns displayed on the inside walls of large cylindrical enclosures also causes a higher incidence of strabismus. Histologically and electrophysiologically, their cortices are quite normal in their binocularity. This development of a horizontal strabismus in the presence of a binocularly organized cortex may be explained by the lack of one outstanding (dominating) pair of vertical contours in the surroundings of these animals. The authors are presently engaged in studies aimed at determining the minimum amount of exposure to repetitive patterns necessary to keep up fairly normal cortical binocularity. They hope to develop a simple regimen of visual "treatment" that could be employed with very young children exhibiting strabismus before the age at which surgical alignment can be accurately performed. (3 figures, 30 references)—Peter C. Kronfeld

NEWER METHODS OF INVESTIGATING STRABISMUS. Mein, J. (Hallamshire Hosp., Sheffield, England). Br. J. Ophthalmol. 58:232, 1974.

The alternate prism cover test still yields the most useful measurements of manifest deviations. Combined with concave lenses, while accommodation is carefully maintained at six meters, the prism cover test also proves to be the most reliable method for measuring the AC/A ratio. In the follow-up on patients with amblyopia near vision can be more revealing than distance vision. The Hess screen, in its original or modified form, combined with mapping of the field of binocular fixation (with the conventional round 2 mm target as well as with a linear target), is still the most useful method for recording ocular movements in paralytic squint. The tracking of saccadic movements by electro-oculography may turn out to be a practical method for the recognition of a paralytic nature or component of strabismus in children and very elderly patients. Irvine's four-diopter prism test for the assessment of binocular function is not an easy test to perform or to interpret. Bagolini's striated glasses (plano glasses with an almost invisible striation, usually placed in the 45 degree position before one eye and in the 135 degree position before the other eye) probably represent the most practical test for the type of interocular sensory relationship in children. The test is done for distance and for near, and the children should be asked to draw what they see. The great advantage of Jampolsky's prism adaptation test (with Fresnel prisms) lies in that time is allowed for the process of adaptation to occur and to be observed. Lang's test for gross stereopsis—the child having to place the bottom of a pencil on top of a second pencil held and moved by the examiner—has been a valuable addition to the orthoptist's armamentarium. Most children with strabismus have no difficulty in doing this test with both eyes open. The test is then repeated with the squinting eye occluded; unequivocally poorer performance on the second test points toward anomalous correspondence. No difference in performance speaks for suppression of the image of the squinting eye. (3 figures, 12 references)—Peter C. Kronfeld

FAMILY STUDIES IN GLAUCOMA. Perkins, E. S. (Inst. Ophthalmol., Univ. of London, London). Br. J. Ophthalmol. 58:529, 1974.

Among 190 siblings, sons or daughters of patients with primary open-angle glaucoma ten cases of elevated pressure, glaucomatous field defects and suspicious or definitely cupped disks were identified. In the same group of 190 individuals there were also found four cases of elevated pressure associated with other abnormalities of aqueous dynamics or with cupped disks; another 53 individuals in the same group showed either elevated pressure or suspicious disks. Similarly, among 67 first-degree relatives of patients with known angle-closure glaucoma four cases of the same disease were identified. The prevalence rates for both types of glaucoma increased substantially if individuals under 40 years of age were excluded from the calculation. A similarly high prevalence rate seemed to apply to low-tension glaucoma. No cases of glaucoma were found in the more distant relatives. The results confirm previous reports of a high familial incidence of primary

open-angle and angle-closure glaucoma. (8 tables, 10 references)—Peter C. Kronfeld

MANAGEMENT OF THE DRY EYE IN SJØGREN'S SYNDROME. Williamson, J., Doig, W. M., Forrester, J. V., Tham, M. H., Wilson, T., Whaley, K., and Dick, W. C. (Eye Dept., Southern General Hosp., Glasgow, Scotland). Br. J. Ophthalmol. 58:798, 1974.

Ninety-eight patients suffering from keratoconjunctivitis sicca (KCS) were observed for five or more years. The course of the disease was assessed from subjective symptoms and objective, mostly biomicroscopic findings brought out by staining with Rose bengal and fluorescein. The basic therapy on which all patients were started, consisted of frequent instillations of an alkaline tear substitute. Sixty-four patients could be carried on this treatment for the entire five-year period, with 44 of them assessed as subjectively and objectively improved. If, by the end of the first year, signs or symptoms had increased in severity, the treatment was changed. In 30 such cases the lacrimal canaliculi were obliterated by diathermy; three years later 21 of these patients were judged to have benefited, subjectively and objectively, from the conservation of their own tear fluid, while two had deteriorated further. If, after one year of basic therapy or of blocked outflow of tears, the KCS was essentially unimproved and if mucous threads and corneal filaments were a prominent finding, mucolytic therapy in the form of acetyl-cystein instillations was instituted. After one year of treatment with this agent six out of 20 patients were regarded as improved, both subjectively and objectively. Antibiotics in the form of chloramphenicol four times a day were given to all new patients during the first month of basic treatment, and continued or reinstated as signs of bacterial infection came to the fore. Susceptibility to recurrent staphylococcic infections seemed to be a characteristic of a small group of patients and calls for special vigilance. (3 figures, 5 tables, 15 references)—Peter C. Kronfeld

PATHOGENESIS OF HYPERTENSIVE RETINOPATHY. AN EXPERIMENTAL STUDY IN THE MONKEY. Garner, A., Ashton, N., Tripathi, R., Kohner, E. M., Bulpitt, C. J., and Dollery, C. T. (Dept. Pathol., Inst. Ophthalmol., Univ. of Londor [London]. Br. J. Ophthalmol. 59:3, 1974.

An acute form of cardiovascular hyperten sion was produced in young cynomolgus monkeys by surgical procedures aimed at reduction of the renal blood flow. The animals were observed clinically, including fundus photography and fluorescein fundus angiography, for periods up to four months. There was fair correlation between the rises in blood pressure and the severity of the retinopathy. The earliest signs of the latter were fluorescein-leaking spots on small arteries and arterioles. Cotton-wool spots came next, closely related to places of fluorescein leaks. Synchronous with but less prominent than the cotton-wool spots were linear or flame-shaped retinal hemorrhages. In the severely affected animals waxy exudates formed relatively late in the deep layers of the retina and in the shape of a star in the macula. The focal and general narrowing of the arterial tree which is so characteristic of accelerated hypertension in man was not observed. Instead, the large vessels became tortuous and measurably dilated. Fluorescein angropophy however, did demonstrate arteriolar occlusion in some areas of cotton-wool spots. These areas stood out by their failure to fill during the early phases, and by irregular filling plus marked leakage in the late phases. Pathological evidence of vascular disease, at the time the animals were sacrificed, was most prominent in the kidneys and in the retina, reflecting the generally early state of the disease at which the experiments were terminated. The condition of the arteries was found to vary from normality to severe necrosis. Many precapillary arteries were constricted and some were virtually occluded. In the walls of these vessels the smooth muscle layer was most clearly and severely affected, and there the process of insudation could be observed; plasma had seeped into the muscular coat, sometimes entirely displacing the smooth muscle cells. From these findings the authors propose the following sequence of pathological processes: the retinal arterioles, in the process of autoregulation, respond to the rise in blood pressure with constriction to such a degree that the muscle tissue within the vessel wall becomes necrotic. This wall is now unsupported and allows insudation which then becomes the main factor in the occlusion of the vessel, under the pathological picture of fibrinoid necrosis. (44 figures, 4 tables, 86 references)—Peter C. Kronfeld

Journal of Neurosurgery

PITUITARY APOPLEXY IN A CHILD. Sakalas, R., David, R. B., Vines, F. S., and Becker, D. P. (Div. Neurosurg., Virginia Commonwealth University Health Sciences Division, Richmond, Va.). J. Neurosurg. 39:519, 1973.

A rapidly growing 6-year-old boy with progressive visual loss suddenly became blind following an acute hemorrhage into an eosinophilic adenoma. Vision in his better eye was restored following prompt neurosurgical intervention. (3 figures, 8 references)—Joel G. Sacks

PUPILLARY SPARING IN OCULOMOTOR PALSY FROM INTERNAL CAROTID ANEURYSM. Kasoff, I., and Kelly, D. L. (Section Neurosurg., Bowman Gray School Med., Winston-Salem, N.C.). J. Neurosurg. 42: 713, 1975.

A pupil-sparing oculomotor nerve palsy is unlikely to be produced by an intracranial aneurysm. However, a 54-year-old man developed such an incomplete palsy and was found to have a carotid-posterior communicating aneurysm. The mechanism of the pupillary sparing appears to be based on the relative positions of the parasympathetic fibers within the subarachnoid portion of the third nerve and the aneurysm. (4 figures, 23 references)—Joel G. Sacks

Mayo Clinic Proceedings

OPEN-ANGLE GLAUCOMA ASSOCIATED WITH TOPICAL ADMINISTRATION OF FLURANDRENOLIDE TO THE EYE. Brubaker, R. F., and Halpin, J. A. (Mayo Graduate School Med., Univ. Minnesota, Rochester, Minn.). Mayo Clin. Proc. 50:322, 1975.

Intraocular pressure was elevated in both eyes and a glaucomatous field defect developed in one eye of an 18-year-old Caucasian man after prolonged topical use of flurandrenolide. (3 figures, 34 references)—Authors' abstract

Mount Sinai Journal of Medicine, New York

THE PRESENT STATE OF TOXOPLASMOSIS. Szabo, T. (Dept. Surgery, Mt. Sinai School Med., New York, N.Y.). Mt. Sinai J. Med. NY 41:765, 1974.

Toxoplasma gondii is a coccidian parasite and like most other coccidia it has an enteroepithelial cycle in a specific host, resulting in formation of occysts.

The modes of transmission are carnivorism, fecal contamination, and transplacental or congenital infection. Infective oocysts have been isolated from naturally contaminated soil. Land snails and earthworms, flies, and cockroaches may serve as an intermediate host. Five to 15% of babies with congenital toxoplasmosis die and 10 to 13% have moderate to marked visual damage; 58 to 72% are clinically normal at birth. (2 figures, 2 tables, 30 references)—Joel G. Sacks

Neurology

OCULAR FLUTTER AND DOWNBEAT NYSTAGMUS: A CASE WITH SUPRATENTORIAL ORIGIN. Senelick, R. C., Ajax, E. T., and Van Dyk, J. L. (Dept. Neurology and Division Ophthalmol., Univ. of Utah College Med., Salt Lake City, Utah). Neurology 24:1109, 1974.

A 56-year-old man was found to have ocular flutter, downbeat nystagmus, and frontal ataxia. Pathologic examination revealed a right fronto-temporal glioblastoma involving the fronto-ponto-cerebellar pathways. The brain stem and cerebellum were free of lesions. It is reasonable to assume that ocular flutter and downbeat nystagmus may arise with interruption of cortico-pontine pathways. (2 figures, 11 references)—Joel G. Sacks

DOES PSEUDOTUMOR CEREBRI CAUSE THE EMPTY SELLA SYNDROME? Foley, K. M., and Posner, J. B. (Neuropsychiatric Service, Memorial Sloan-Kettering Cancer Ctr., New York, NY). Neurology 25:565, 1975.

Eight patients had both the "primary empty sella syndrome," diagnosed by the finding of

an air-filled sella turcica at pneumoencephalography, and pseudotumor cerebri, diagnosed by the finding of an elevated cerebrospinal fluid pressure in the presence of normal ventricular size and position on pneumoencephalography. These two clinical disorders appear to be frequently related, and when they are related, visual field defects and visual loss are more likely to occur than when either entity appears alone. Chronically increased intracranial pressure from pseudotumor cerebri may produce an empty sella if the diaphragma sella is incompetent and the subarachnoid space herniates into the sella turcica. (2 figures, 1 table, 29 references)—Authors' abstract

SPONTANEOUS INFARCTION IN PITUITARY TUMORS: NEUROLOGIC AND THERAPEUTIC ASPECTS. Conomy, J. P., Ferguson, J. H., Brodkey, J. S., and Mitsumoto, H. (Div. Neurology, Div. Neurosurg., Case Western Reserve Univ. Medical School, Cleveland, Ohio). Neurology 25:580, 1975.

In addition to progressive endocrine dysfunction and progressive visual loss, pituitary neoplasms may announce their presence by the more catastrophic alternative of spontaneous tumor infarction. In two patients reported, illness due to the spontaneous infarction of pituitary tumors was heralded by sudden onset of focal headache associated with diplopia. Stupor, confusion, and evidence of increased intracranial pressure occurred without subarachnoid hemorrhage or massive extrasellar extension of tumor. In both patients, skull x-rays suggested a long-standing intrasellar mass. Both underwent prompt treatment with endocrinologic replacement therapy and subsequent successful transsphenoidal removal of voluminous, infarcted, pituitary masses. (5 figures, 2 tables, 29 references)—Authors' abstract

TRANSACTIONS OF THE AMERICAN OPHTHALMOLOGICAL SOCIETY

TRANSILLUMINATION OF THE IRIS. Donaldson, D. D. (Boston, Mass.). Trans. Am. Ophthalmol. Soc. 72:89, 1974.

Translucency of the iris is sufficiently characteristic in a number of pathological conditions to make it a useful diagnostic sign. The uniform and almost total translucency of the iris in albinism is characteristic. Even in the carrier state involvement is very extensive except for the sphincter region. A variable degree of translucency is found in about a third of the severe diabetics and in the more advanced cases a stippled effect is characteristic. In pigmentary glaucoma an almost pathognomonic finding is that of radial or spokelike transillumination of the outer half of the iris. Involvement of only the pupillary margin is usually seen in pseudoexfoliation and is indistinguishable from senile changes in iris translucency. In long-standing chronic glaucoma, involvement of the peripheral iris as well as the pupillary border is found and thus this is not felt to be merely a senile change. Chronic uveitis typically has localized areas of pigment epithelial loss which may or may not be associated with stromal iris atrophy. (14 figures, 9 references)—Author's abstract

FURTHER OBSERVATIONS ON ATYPICAL BAND KERATOPATHY IN GLAUCOMA PATIENTS. Kennedy, R. E., Roca, P. D., and Platt, D. S. (Div. Ophthalmol., Univ. Rochester School Med., Rochester, N.Y.) Trans. Am. Ophthalmol. Soc. 72:107, 1974.

The authors report 48 glaucoma patients who developed band keratopathy. These patients were all on the same medication and on investigation it turned out that the medications all contained phenylmercuric nitrate as a preservative. Phenylmercuric nitrate in some manner promotes the deposition of calcium in the cornea giving rise to band keratopathy. Treatment consists of substituting a solution that does not contain phenylmercuric nitrate and using a chelating agent to remove deposits that interfere with vision. (6 figures, 11 references)—David Shoch

PHOTOCOAGULATION AS A TREATMENT OF EPITHELIAL IMPLANTATION CYSTS FOLLOWING CATARACT SURGERY. Okun, E., and MANDELL, A. (Washington Univ. School Med., St. Louis, Mo.). Trans. Am. Ophthalmol. Soc. 72:170, 1974.

Three patients developed epithelial implantation cysts after cataract surgery. These were treated with photocoagulation. Four to six treatments were needed in each case to obliterate these cysts. (2 figures, 18 references)—David Shoch

PROGRESSIVE CHANGES IN THE ANGLE IN CONGENITAL ANIRIDIA, WITH DEVELOPMENT OF GLAUCOMA. Grant, W. M., and Walton, D. S. (Boston, Mass.). Trans. Am. Ophthalmol. Soc. 72:207, 1974.

Over a period of 18 years the authors have followed a group of 60 children with congenital aniridia—31 of whom had glaucoma. The glaucoma gradually develops over a period of years and this is due to the fact that all children with aniridia do in fact have a peripheral stump of iris present. Some of these children have irregular fine attachments of the iris stroma into the angle wall. In those children who develop glaucoma the anterior stromal layer of the iris stump gradually extends anteriorly to the trabecular meshwork and the intraocular pressure becomes elevated as the filtration area becomes covered by the extension of abnormal iris tissue. The detachment of this iris tissue surgically may stop the progression of the glaucoma. (26 references) —David Shoch

NANOPHTHALMOS WITH UVEAL EFFUSION: A NEW CLINICAL ENTITY. Brockhurst, R. J. (Retina Foundation, Boston, Mass.). Trans. Am. Ophthalmol. Soc. 72:371, 1974.

Five cases are presented all of whom had smaller than normal eyes. Their corneal diameters were about 10 mm while the globe diameters were from 13 to 17 mm. All these patients were highly hyperopic and developed glaucoma in the fourth to sixth decade of life. These particular patients are unusual in that they also developed uveal effusions. This type of uveal effusion is best treated with steroids rather than with operative intervention. (26 figures, 15 references)—David Shoch

REACTION OF THE RABBIT RETINAL PIGMENT EPITHELIUM TO SYSTEMIC LEAD POISONING. Brown, D. V. L. (Dept. Ophthalmol., Rush Medical College, Chicago, Ill.). Trans. Am. Ophthalmol. Soc. 72:404, 1974.

Chronic ingestion of inorganic lead by albino and pigmented rabbits for up to two years produced primarily a microscopic retinal pigment epitheliopathy. No changes were observable by ophthalmoscopy or fluorescein angiography. Further, functional studies including electroretinography and electrooculography were entirely normal at all stages. The major microscopic change was accumulation of light brown granules within the cytoplasm of the retinal pigment epithelium cells. (15 figures, 2 tables, 93 references)—David Shoch

CONGENITAL STATIONARY NIGHTBLINDNESS. Carr, R. E. (Dept. Ophthalmol., New York University Med. Ctr., New York, N.Y.). Trans. Am. Ophthalmol. Soc. 72: 448, 1974.

The various forms of congenital stationary nightblindness (CSNB) are presented and can be divided into those with normal fundi and those in which the fundus is abnormal. On the basis of electrophysiologic and psychophysical tests, as well as a study of the visual pigments in vivo, the basic abnormality in these disorders can be suggested. In the disorders with normal fundi as well as Oguchi's disease, visual pigments are normal both in amount and kinetics, and the basic abnormality seems one of neural transmission at certain levels of the outer retina. In fundus albipunctatus, visual pigment kinetics and electrophysiologic tests of retinal function are greatly retarded and the basic defect in this disorder seems one of retardation in the formation of the visual pigments. (15 figures, 92 references)—Author's abstract

INDENTATION GONIOSCOPY AND EFFICACY OF IRIDECTOMY IN ANGLE-CLOSURE GLAUCOMA. Forbes, M. (Columbia-Presbyterian Med. Ctr., New York, N.Y.). Trans. Am. Ophthalmol. Soc. 72:488, 1974.

Iridectomy was performed on 227 eyes of 151 patients with primary angle-closure glaucoma. Before surgery an estimate of the extent of synechial closure was made by indentation gonioscopy. Generally one could predict the success of iridectomy by the degree of synechial closure. The outlook for success is favorable for eyes with 0 to 50% peripheral anterior synechias and unfavorable for eyes with 80 to 100% peripheral anterior synechias. In the intermediate range, 55 to 75% peripheral anterior synechias, the outlook is uncertain and all other relevant factors must be considered before arriving at a surgical decision. In equivocal situations it may be preferable to

try the safer iridectomy first with an understanding that a secondary operation might be needed afterward. (5 figures, 2 tables, 81 references)—David Shoch

THE NATURE OF HEREDITARY DEEP POLYMORPHOUS OF THE CORNEA: ITS ASSOCIATION WITH IRIS AND ANTERIOR CHAMBER DYGENESIS. Grayson, M. (Indiana Univ. Med. Ctr., Indianapolis, Ind.). Trans. Am. Ophthalmol. Soc. 72:516, 1974.

Three generations of a family with marked anomalies of the anterior segment of the eye were studied. These anomalies included deep posterior polymorphous changes of the cornea, iris atrophy, iris synechiae, abnormal iris processes, corectopia, prominent ring of Schwalbe, open angle glaucoma, circumscribed posterior keratoconus, corneal edema, cornea guttata, scleral cornea and band-keratopathy. Current evidence seems to implicate a hereditary malformative problem occurring on the posterior surface of the cornea bordering the anterior chamber and chamber angle. The association of deep posterior polymorphous dystrophy with dysgenesis of the anterior segment, band-keratopathy, sclerocornea and glaucoma can cause marked decrease in vision. It is a progressive disease and can be associated with systemic findings. Fortunately, despite the alterations in the anterior segment anatomy, penetrating keratoplasty can be performed successfully in some of these patients. (18 figures, 1 table, 68 references)—David Shoch

OCULAR MELANIN AND THE ADRENERGIC INNERVATION TO THE EYE. Laties, A. M. (Philadelphia, Pa.). Trans. Am. Ophthalmol. Soc. 72:560, 1974.

Iris stromal melanocytes receive both adrenergic and cholinergic innervation. It is probable, but not certain, that choroidal melanocytes are similarly innervated. Tyrosinase, the rate-limiting enzyme in the biosynthesis of melanin, is present both in the iris and in the choroid. Interruption of the sympathetic pathways leads to a rapid decline in the tyrosinase activity in both choroid and iris. The magnitude of the decline of tyrosinase levels was the same in animals in which the superior cervical ganglion had been removed and in animals in which there had been a preganglionic interruption of the sympathetic pathways; in neither case did tyrosinase return to normal in the ensuing months. (13 figures, 6 tables, 56 references)—Author's abstract

MEASUREMENT OF CAPILLARY FUNCTION IN EYE DISEASES. O'Rourke, J. (Div. Ophthalmol., Univ. Connecticut, Farmington, Conn.). Trans. Am. Ophthalmol. Soc. 72:606, 1974.

The author measured capillary function in the eye by measuring the anterior chamber clearance of isotopic xenon. Although the clinical value of this technique is not entirely established there are theoretical advantages which the author lists as follows: (1) Recover new forms of data leading to better definitions of ocular diseases. (2) Provide more reliable data by a continuous recording of dynamic changes in the untouched eye. (3) Furnish specific information about particular tissue functions such as microvascular perfusion. (4) Provide more objective data available in digital form, permitting mathematical analyses during live studies. (5) Quantitate indications of a need for more or different forms of therapy and of responses to them. (13 figures, 5 tables, 79 references)—Author's abstract

ELECTRON MICROSCOPIC HISTOCHEMICAL STUDIES OF CYCLIC 3′, 5′-NUCLEOTIDE PHOSPHODIESTERASE IN THE DEVELOPING RETINA OF NORMAL MICE AND MICE WITH HEREDITARY RETINAL DEGENERATION. Robb, R. M. (Dept. Ophthalmol., Harvard Medical School, Boston, Mass.). Trans. Am. Ophthalmol. Soc. 72:650, 1974.

The occurrence of hereditary retinal degeneration in mice has been known since 1951. Although many morphological and biochemical studies have been done on this condition, none have uncovered the pathophysiology of the disorder, which results in degeneration and disappearance of photoreceptor cells by the end of the third postnatal week. Recent biochemical studies have suggested a deficiency in cyclic nucleotide phosphodiesterase in photoreceptor cells of dystrophic mice, but the timing of this deficiency was such that it was not clear whether the defect was a primary one or one secondary to the failure of photoreceptors to produce more than rudimentary outer segments, the retinal site of highest phosphodiesterase activity. The present histochemical

study demonstrates phosphodiesterase activity in the rudimentary outer segment lamellae of both normal and dystrophic animals, suggesting that the lagging enzyme levels in dystrophic animals are secondary to incomplete cellular development rather than a primary defect. Selected electron microscopic observations on retinal degeneration in the mouse are included as a background for the histochemical work. (13 figures, 48 references)—Author's abstract

TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETIES OF THE UNITED KINGDOM

THE HISTOCOMPATIBILITY ANTIGEN (HL-A 27) AND ACUTE ANTERIOR UVEITIS. Brewerton, D. A. (Westminster Hospital, London). Trans. Ophthalmol. Soc. U.K. 94:735, 1974.

One hundred Caucasian adults with acute anterior uveitis were investigated. This group consisted of 64 men and 36 women. Sixty-two of them were seen within four weeks of the onset of their first attack and 38 had severe recurrent uveitis. Of the 100 patients, 33 had associated diseases and in this group there were 29 patients with positive HL-A 27 antigen. There were 67 patients who had never had any rheumatic symptoms and here again there were 29 patients with positive HL-A 27 antigen. There was no correlation between the presence of HL-A 27 antigen and recurrence of uveitis. (2 tables, 10 references)—David Shoch •

THE EYE IN JUVENILE RHEUMATOID ARTHRITIS. Smiley, W. K. (Canadian Red Cross Memorial Hosp., Taplow, Maidenhead, Berkshire, England). Trans. Ophthalmol. Soc. U.K. 94:817, 1974.

Juvenile chronic polyarthritis occurs in several forms and in two of these is associated with iridocyclitis: (1) An acute, self-limiting, but recurring iridocyclitis occurs in older children, all males in the author's series, and responds well to treatment. They develop an initial polyarthritis which goes on to become a more localized sacroiliitis and eventually, in some, a typical ankylosing spondylitis. The acute ocular inflammation may help to establish the correct diagnosis of the joint condition at an earlier stage than would otherwise be possible. (2) A chronic, insidious, long-lasting iridocyclitis tends to occur at an earlier age, more in girls than in boys, with no systemic disease and only a few joints involved. These children have antinuclear antibodies which may precede the onset of eye inflammation. The visual prognosis is poor despite prolonged treatment; although a small number of eyes may run a more benign course, more than 50% of the rest become blind or partially-sighted. By clinical and serological examination it is at least now possible to identify children at risk and treat their eyes at the first sign of involvement. (4 figures, 2 tables, 13 references)—Author's abstract • • •

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings and lecturers must be received at least three months prior to the date of occurrence.

FIGHT FOR SIGHT, INC.: AWARD APPLICATIONS

Applications for 1976-1977 Fight For Sight, Inc., awards will be accepted between Oct. 15, 1975, and March 1, 1976. Fight For Sight awards include student fellowships, postdoctoral research fellowships, grants-in-aid, and modest departmental awards. The Fight For Sight is particularly receptive to younger investigators with pilot projects. For application forms and additional information, write Secretary, Fight For Sight, Inc., 41 W. 57th St., New York, NY 10019.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY, INC.: REGIONAL MEETINGS

The regional meetings of the Association for Research in Vision and Ophthalmology, Inc., are scheduled as follows: Atlantic Section—Nov. 14 and 15, 1975, Duke University Eye Center, Durham, North Carolina; Central Section—Oct. 24 and 25, 1975, University of Michigan Medical School, Towsley Center, Ann Arbor, Michigan; Southern Section—Nov. 7 and 8, 1975, Holiday Inn (Medical Center), Houston, Texas. The Pacific Section meeting was held Sept. 18 and 19, 1975, University of Oregon Health Sciences Center, Portland, Oregon.

WILLS EYE HOSPITAL: SEVENTH ANNUAL CONFERENCE

The Retina Service of the Wills Eye Hospital and Jefferson Medical College of Thomas Jefferson University will cosponsor a course, "Vascular diseases of the ocular fundus," March 6 and 7, 1976, at Jefferson Hall Commons, Philadelphia. The guest lecturer is Paul Henkind. Tuition for the course, which includes lunches and a dinner, is $175; $60 for residents and fellows. For further information, write Richard E. Goldberg, M.D., Retina Service, Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130. The course meets the criteria for 13 hours of credit in Category I for the Physician's Recognition Award of the American Medical Association.

MICHAEL REESE MEDICAL CENTER: COURSE IN RETINAL VASCULAR AND MACULAR DISORDERS

Michael Reese Medical Center School of Health Sciences and the Department of Ophthalmology will hold a course in the diagnosis and management of retinal vascular and macular disorders Nov. 13-15, 1975, at the Continental Plaza Hotel, Chicago. The fee for the course is $200. For further information and registration, write Ms. Paulette Howard, Department of Ophthalmology, Michael Reese Medical Center, 2900 S. Ellis Ave., Chicago, IL 60616.

THE WILMER INSTITUTE: COURSE IN DISEASES AND SURGERY OF THE ANTERIOR SEGMENT

The Wilmer Institute will offer a course in external ocular diseases and anterior segment surgery Nov. 13-15, 1975, at the Johns Hopkins Hospital, Baltimore. Speakers will include A. Edward Maumenee, Dan B. Jones. and the faculty of the Wilmer Institute. The course is approved for 16 credit hours in Category I of the American Medical Association. Registration fee is $125. For further information, write Walter J. Stark, M.D., Course Chairman, Wilmer Institute, Johns Hopkins Hospital, Baltimore, MD 21205.

STATE UNIVERSITY OF NEW YORK UPSTATE MEDICAL CENTER: 26TH ANNUAL POSTGRADUATE COURSE IN OPHTHALMOLOGY

The Department of Ophthalmology of the State University of New York Upstate Medical Center in Syracuse will present its 26th annual postgraduate course in ophthalmology at the Hotel Syracuse, Dec. 5 and 6, 1975. Tuition is $50, payable to the State University of New York Upstate Medical Center in Syracuse. The course is limited to 100 participants, accepted in the order in which applications, accompanied by checks, are received. For

further information, write James L. McGraw, M.D., 750 E. Adams St., Syracuse, NY 13210.

Heed Ophthalmic Foundation: Officers

At the last board of directors meeting of the Heed Ophthalmic Foundation May 30, 1975, the following officers were elected: Frank W. Newell, chairman; David Shoch, executive secretary-treasurer; Charles Campbell, Claes Dohlman, and Samuel McPherson, Jr., board members.

American Ophthalmological Society: New Officers

At the recent meeting of the American Ophthalmological Society, May 29-31, 1975, the following officers were elected: Joseph A. C. Wadsworth, president; David O. Harrington, vice-president; Robert W. Hollenhorst, secretary-treasurer; Thomas P. Kearns, editor of the Transactions; and A. Edward Maumenee, councillor.

The Howe Medal was awarded to Michael J. Hogan, professor of ophthalmology, emeritus chairman of the Department of Ophthalmology and head of the Proctor Foundation, University of California, San Francisco, and vice-president of the Ophthalmic Publishing Co.

Pennsylvania Academy of Ophthalmology and Otolaryngology: New Officers

The Pennsylvania Academy of Ophthalmology and Otolaryngology announced the following newly elected or reelected officers: Louis E. Silcox, president; Paul A. Cox, president-elect; William K. Grove, treasurer; Donald B. Kamerer, secretary. The next annual meeting will take place May 19-22, 1976.

Personals

Steven M. Podos

Steven M. Podos has been appointed professor and chairman of the Department of Ophthalmology, Mount Sinai School of Medicine, New York City, and director of the department and ophthalmologist-in-chief. Dr. Podos was formerly professor of ophthalmology at Washington University School of Medicine, St. Louis.

William F. Raub

William F. Raub has been appointed associate director for extramural and collaborative programs of the National Eye Institute. Dr. Raub replaces George T. Brooks, who joined the National Institute of Arthritis, Metabolism, and Digestive Diseases as associate director for extramural program activities.

Dr. Raub was formerly chief of the Biotechnology Resources Branch of the National Institutes of Health Division of Research Resources.

Dr. Raub is a graduate of Wilkes College in Wilkes-Barre, Pennsylvania, and received his Ph.D. from the University of Pennsylvania. Before coming to the National Institutes of Health in 1966, he served as an instructor and postdoctoral fellow in the Department of Physiology at the university's medical school.

• • •

FIVE-YEAR OPHTHALMIC MEETING CALENDAR

For listings, write Bruce E. Spivey, M.D., Professor and Chairman, Pacific Medical Center, Department of Ophthalmology, P.O. Box 7999, San Francisco, CA 94120.

1975

OCTOBER	5-11	World Medical Association Annual Meeting	Tokyo
	13-17	American College of Surgeons, Clinical Congress	San Francisco
	19-22	American Board of Ophthalmology (oral)	Philadelphia
	19-24	Tenth Congreso Argentino de Oftalmologia	Buenos Aires
NOVEMBER	2-6	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
	12-15	International Symposium on Cataracts	Iowa City
	29-DEC. 4	American Medical Association, Clinical Convention	Honolulu

1976

JANUARY	6-15	Dedication, new facilities, Bascom Palmer Eye Institute	Miami
	17	American Board of Ophthalmology (written)	Multiple sites
		Ophthalmic Knowledge Assessment Program, AAOO (written)	Multiple sites
APRIL	5-9	European Congress of Ophthalmology	Hamburg, Germany
	28-May 1	II World Congress on the Cornea	Washington, D.C.
MAY	7-10	American Board of Ophthalmology (oral)	Philadelphia
	14-16	American Ophthalmological Society	Kilauea, Hawaii
	16-21	Pacific Coast Oto-Ophthalmological Society	Seattle
JUNE	13-19	Club Jules Gonin Meeting	Lausanne, Switzerland
	26-JULY 1	American Medical Association, Annual Convention	Dallas
AUGUST	8-13	Asia Pacific Academy of Ophthalmology	Denpasar, Bali, Indonesia
SEPTEMBER	12-16	American Academy of Ophthalmology and Otolaryngology	Las Vegas (tentative)
OCTOBER	11-15	American College of Surgeons, Clinical Congress	Chicago
	21-24	American Board of Ophthalmology	San Francisco
NOVEMBER	11-15	Association of American Medical Colleges	San Francisco
DECEMBER	2-5	American Board of Ophthalmology (oral)	Chicago
	4-8	American Medical Association Clinical Convention	Philadelphia

1977

MARCH	20-25	XI Pan American Congress of Ophthalmology	Santiago, Chile
APRIL	24-28	Pacific Coast Oto-Ophthalmological Society	Tucson, Arizona
MAY	4-7	American Board of Ophthalmology (oral)	San Francisco
	15-20	Instituto Barraquer VII International Course	Barcelona
	30-JUNE 1	American Ophthalmological Society	Hot Springs, Virginia
JUNE	18-23	American Medical Association Annual Convention	San Francisco
OCTOBER	16-19	American Board of Ophthalmology (oral)	Philadelphia
	17-21	American College of Surgeons Clinical Congress	Dallas
NOVEMBER	6-10	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
DECEMBER	4-7	American Medical Association, Interim Convention	Chicago

1978

MAY	14-21	International Congress of Ophthalmology—Concilium Ophthalmologicum Universale	Kyoto, Japan
	29-31	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	16-20	American College of Surgeons Clinical Congress	San Francisco
NOVEMBER	5-9 (tentative)	Association of American Medical Colleges	New Orleans

1979

MAY	28-30	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	22-26	American College of Surgeons Clinical Congress	Chicago
NOVEMBER	4-8	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.

British Journal of Ophthalmology

May 1975 Vol. 59 No. 5

Editorial: Non-drainage of subretinal fluid

Role of non-drainage of subretinal fluid in re-operation for retinal detachment. *P. K. Leaver, A. H. Chignell, L. G. Fison, J. R. Pyne, and S. H. Saunders*

Intravitreal hyaluronic acid injection. A long-term clinical evaluation. *J. J. Kanski*

Angoid streaks, I. Ophthalmoscopic variations and diagnostic problems. *J. A. Shields, J. L. Federman, T. L. Tomer, and W. H. Annesley, Jr.*

Angioid streaks and traumatic ruptures of Bruch's membrane. *A. Hagedoorn*

Aqueous humour lactic dehydrogenase isoenzymes in retinoblastoma. *J. Kabak and P. E. Romano*

HL-A 27 and acute anterior uveitis. *R. Mapstone and J. C. Woodrow*

Medulloepithelioma involving the iris. *A. T. Morris and A. Garner*

Lacrimal immunoglobulins and complement qualified by counter-immunoelectrophoresis. *R. Bluestone, D. L. Easty, L. S. Goldburg, B. R. Jones, and T. H. Pettit*

Urea in the treatment of epibulbar malignancies. *E. D. Danopoulos, G. A. Chiotis, I. E. Danopoulou, and S. B. Liaricos*

Peritoneal autografts in conjunctival replacement. *J. R. O. Collin*

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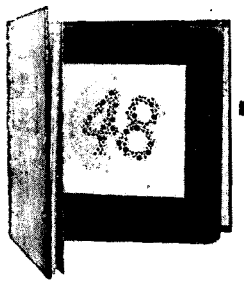
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THE DEPARTMENT OF OPHTHALMOLOGY
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PRESENTS

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THURSDAY AND FRIDAY, NOVEMBER 20 and 21, 1975

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Dr. Norman Schatz
Dr. George Udvarhelyi
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B. *STRABISMUS SYMPOSIUM*

January 9-10, 1976

Guest Lecturers

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Dr. Edward Dunlap
Dr. Alfred Huber
Dr. Arthur Jampolsky
Dr. Marshall Parks
Dr. John Pratt-Johnson

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A combined rate for both of the above meetings is offered at $400 for practitioners and $200 for residents upon application from their Department Head.

C. *VITREOUS-RETINAL-CHOROIDAL SYMPOSIUM*

January 12-15, 1976

Present Concepts in Diagnosis and Treatment of Malignant Melanoma of the Choroid
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October 29, 30, 31, 1975

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Professor and Head
Department of Ophthalmology
State University of New York

University of Illinois Faculty

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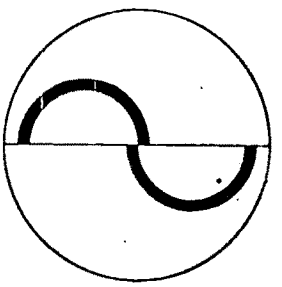
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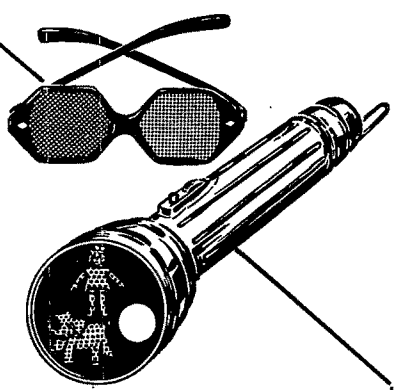
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INFORMATION:

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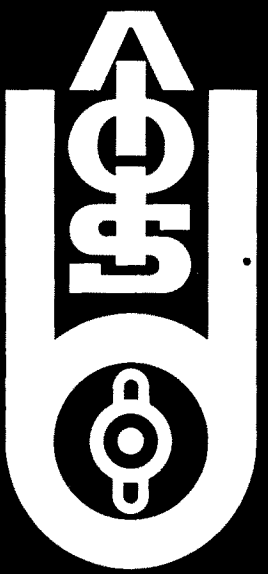
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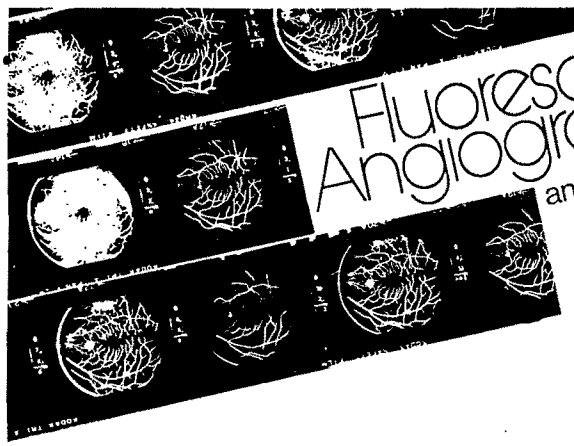
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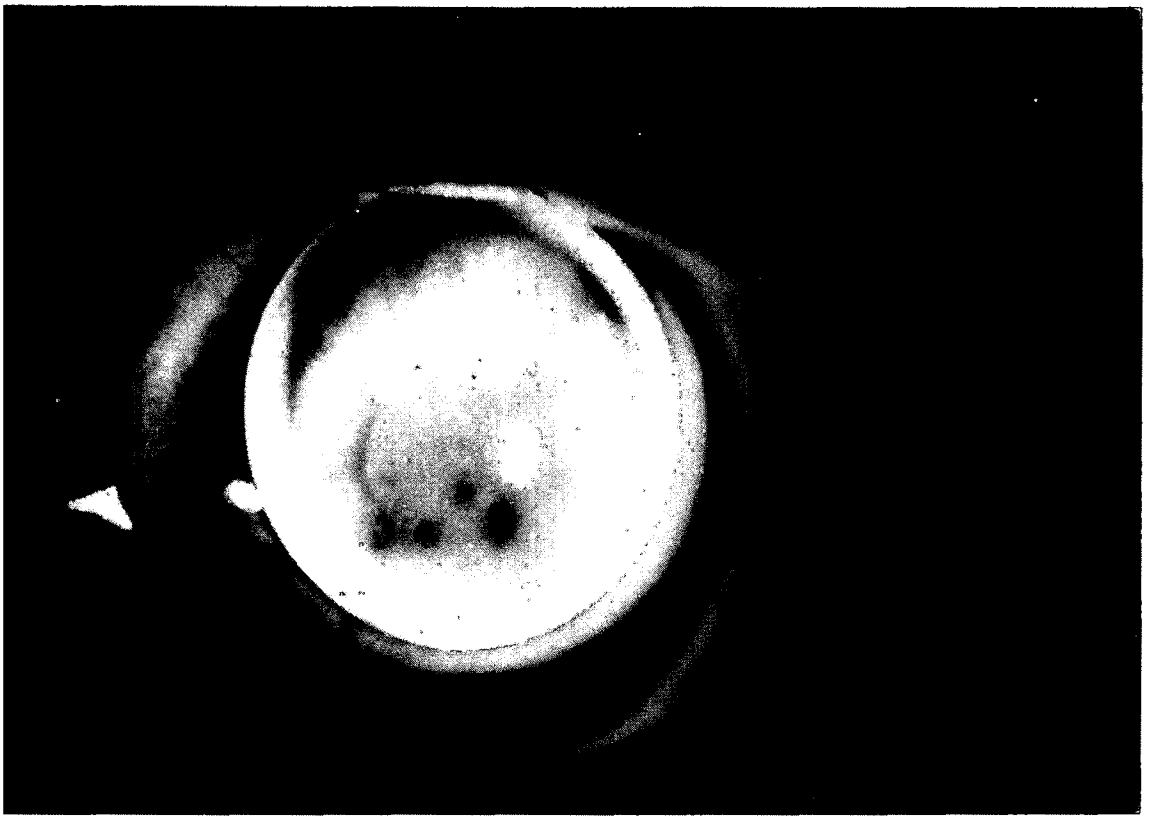
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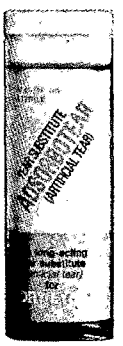
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1. Duke-Elder, S.: Diseases of the Outer Eye, Part I, System of Ophthalmology, Vol. VIII, The C. V. Mosby Co., (St. Louis), 1965, p. 68.

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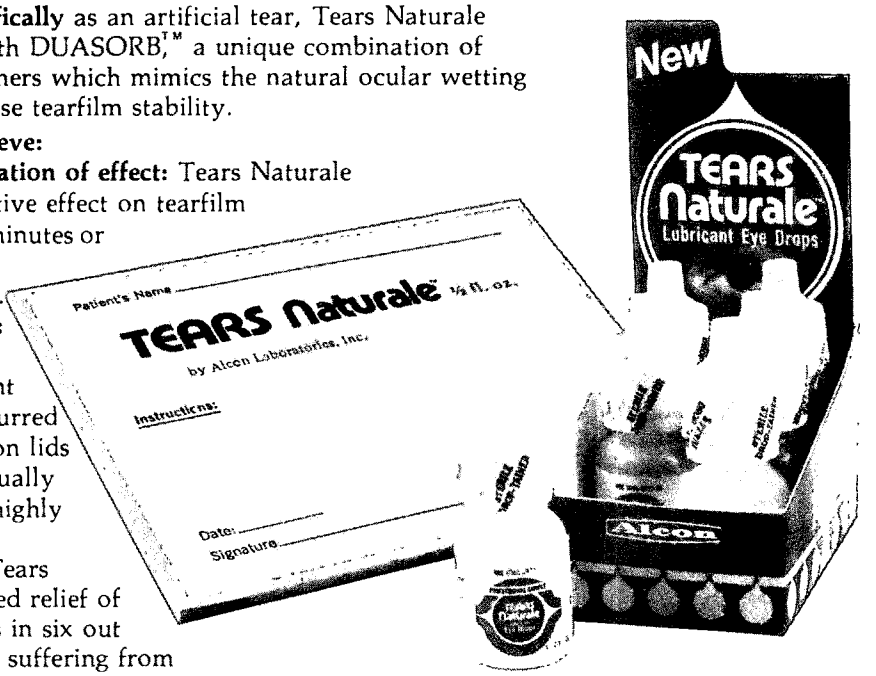
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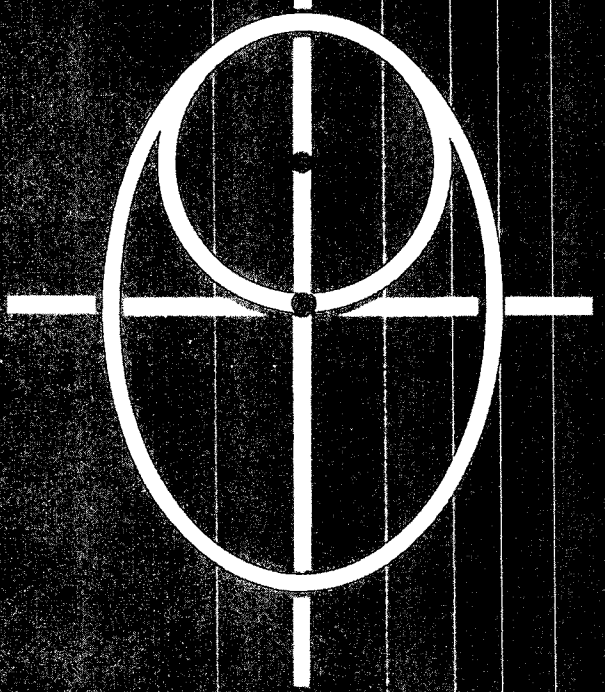
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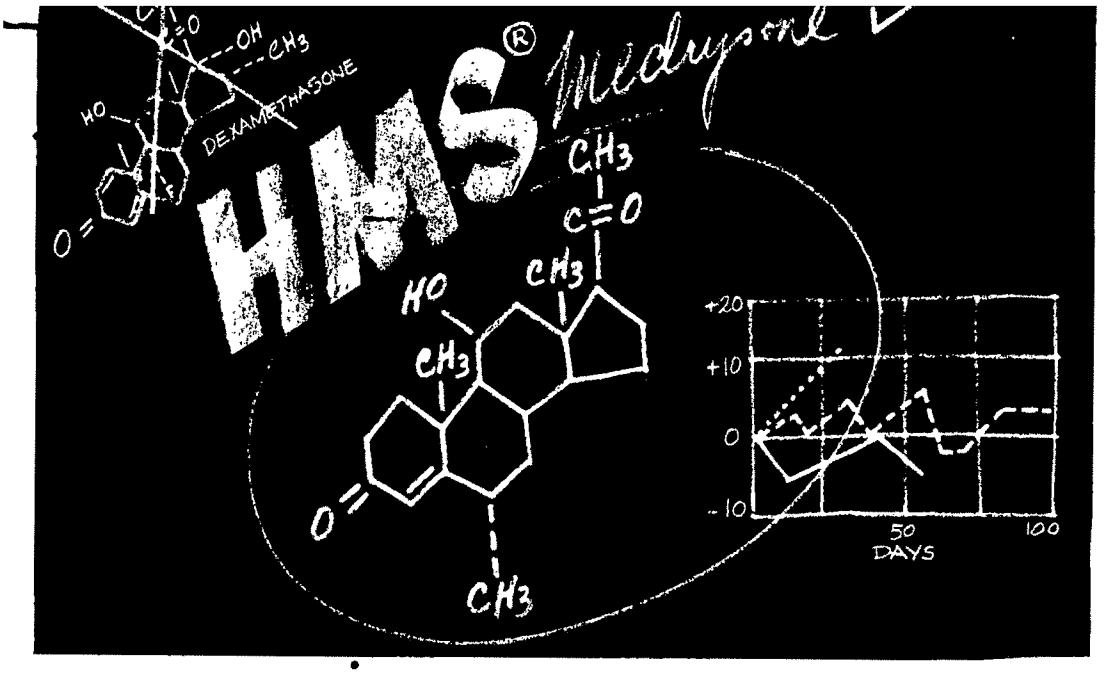


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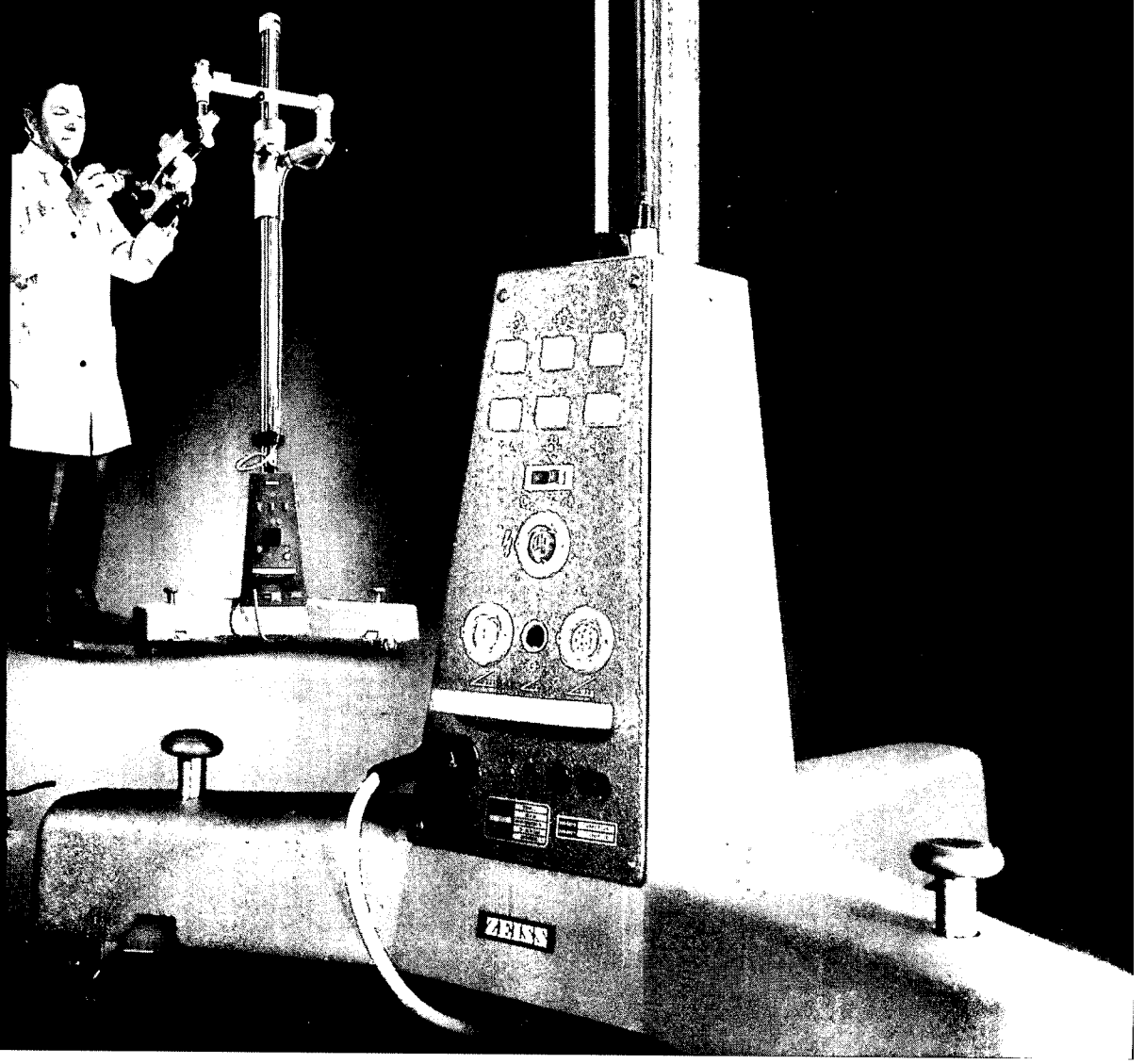
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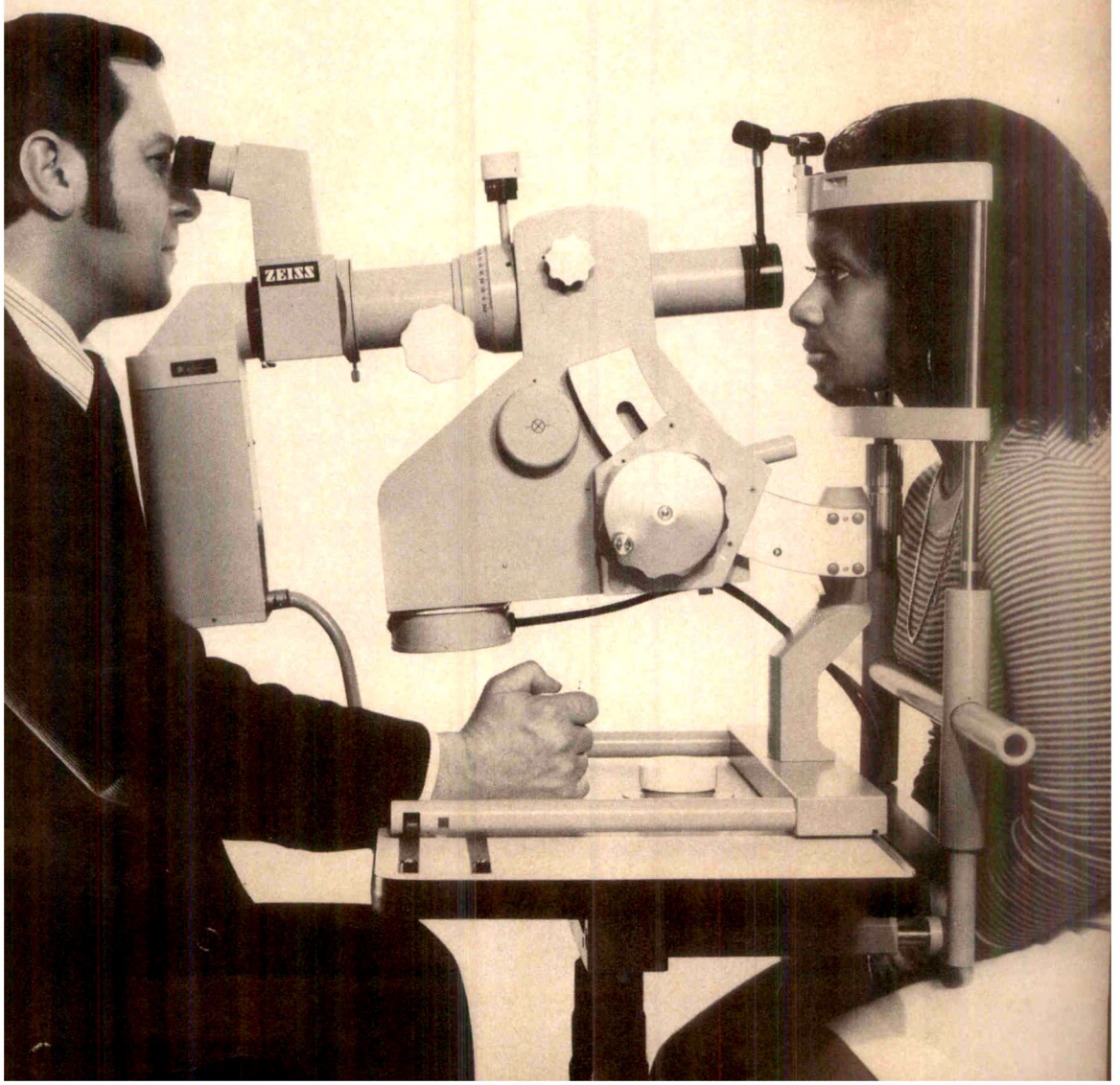
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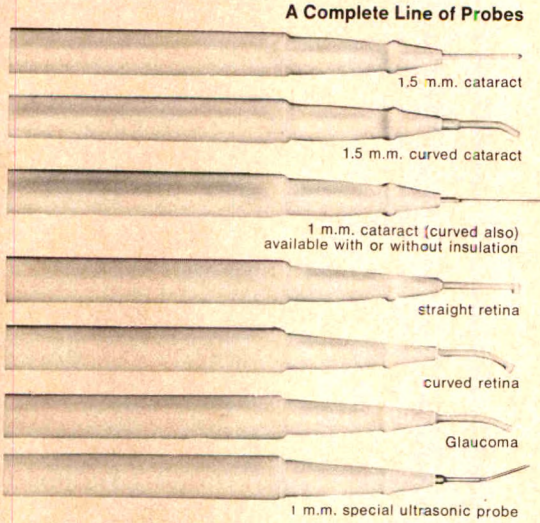
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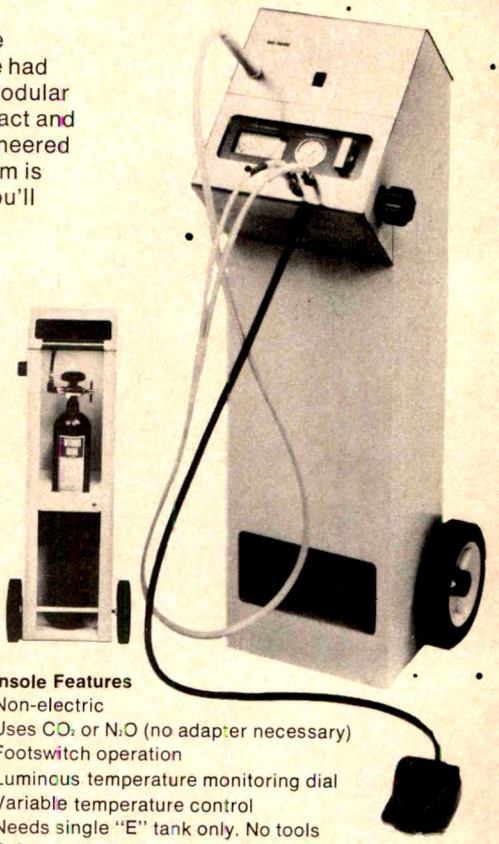
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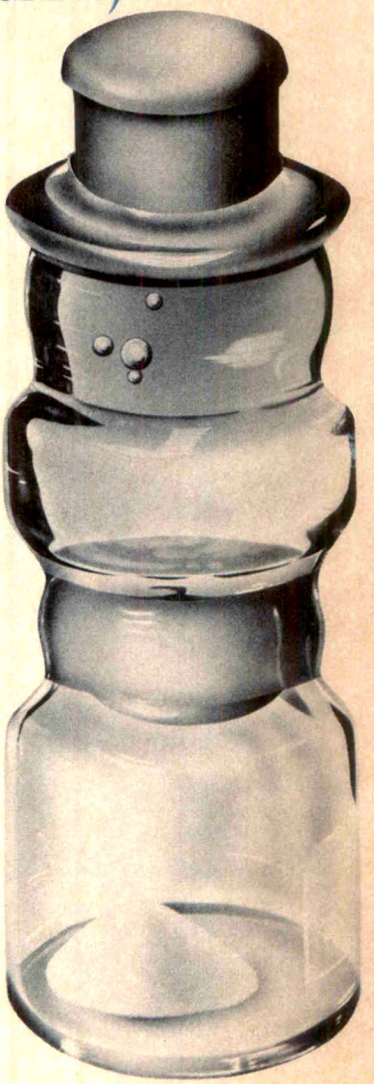
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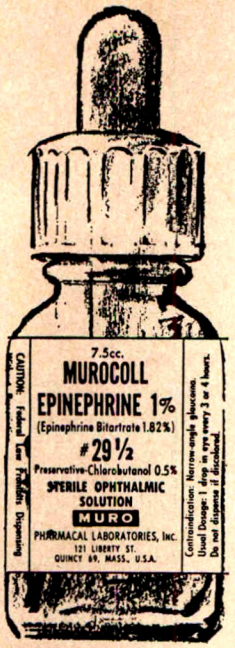
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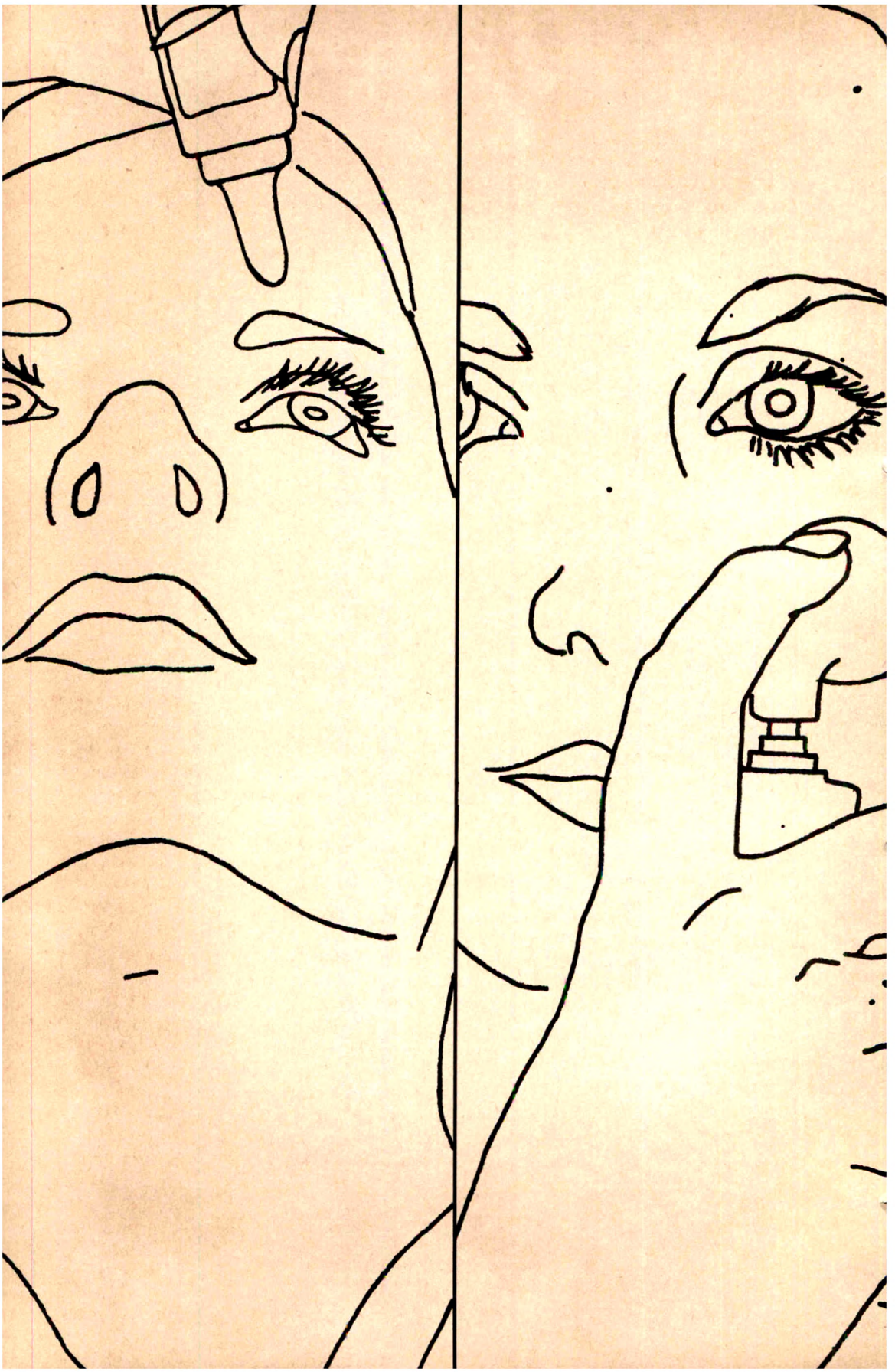
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Recommend Lacri-Lube as an adjunct in the therapy of any eye threatened by exposure, dehydration or desensitization...
All it can do is help. ALLERGAN Irvine, Ca.

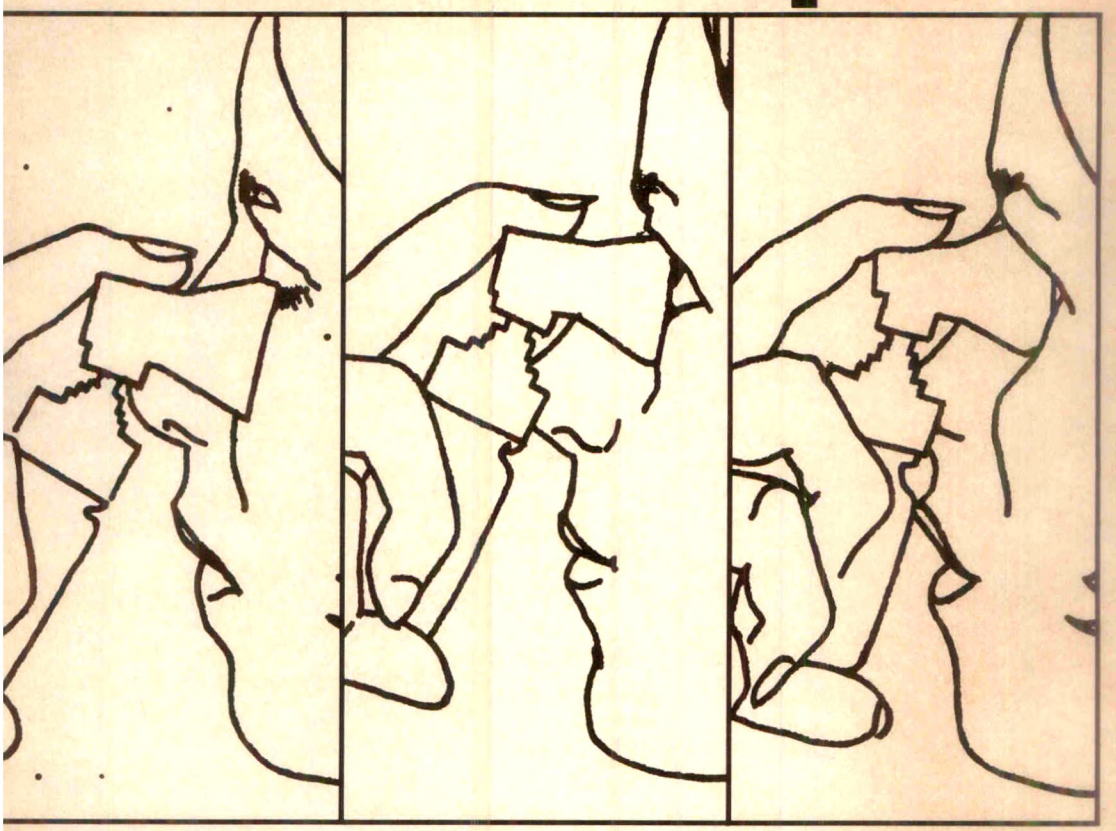


Number two in a series of graphic interpretations by Milton Glaser of ophthalmic conditions for which Lacri-Lube adjunctive therapy is indicated.

Contains: White petrolatum, mineral oil, nonionic lanolin derivatives, chlorobutanol (chloral derivative as preservative) 0.5%. Supplied in 3.5 gm tubes.



A better way to take a drop?



old MISTURA between index nger and thumb. With the eye osed, place top rim of the d-retractor (eyescope) just bove eyelash of upper lid nd use it to gently retract e eyelid.

Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone. Look up within the eye-scope.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.

Used properly, MISTURA can assure complete coverage of the absorbing surface of the eye. Its supraorbital fit avoids eye contact. MISTURA offers easy self-application, economy of full dose, on target delivery, and a minimum of wasted medication.

MISTURA®

Ophthaimic Spray Products



Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965 213-5

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C ***carbachol*** provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with: benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E ***l-epinephrine*** to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for the difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES
1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 as a preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P ***pilocarpine HCl*** is indicated for:
1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

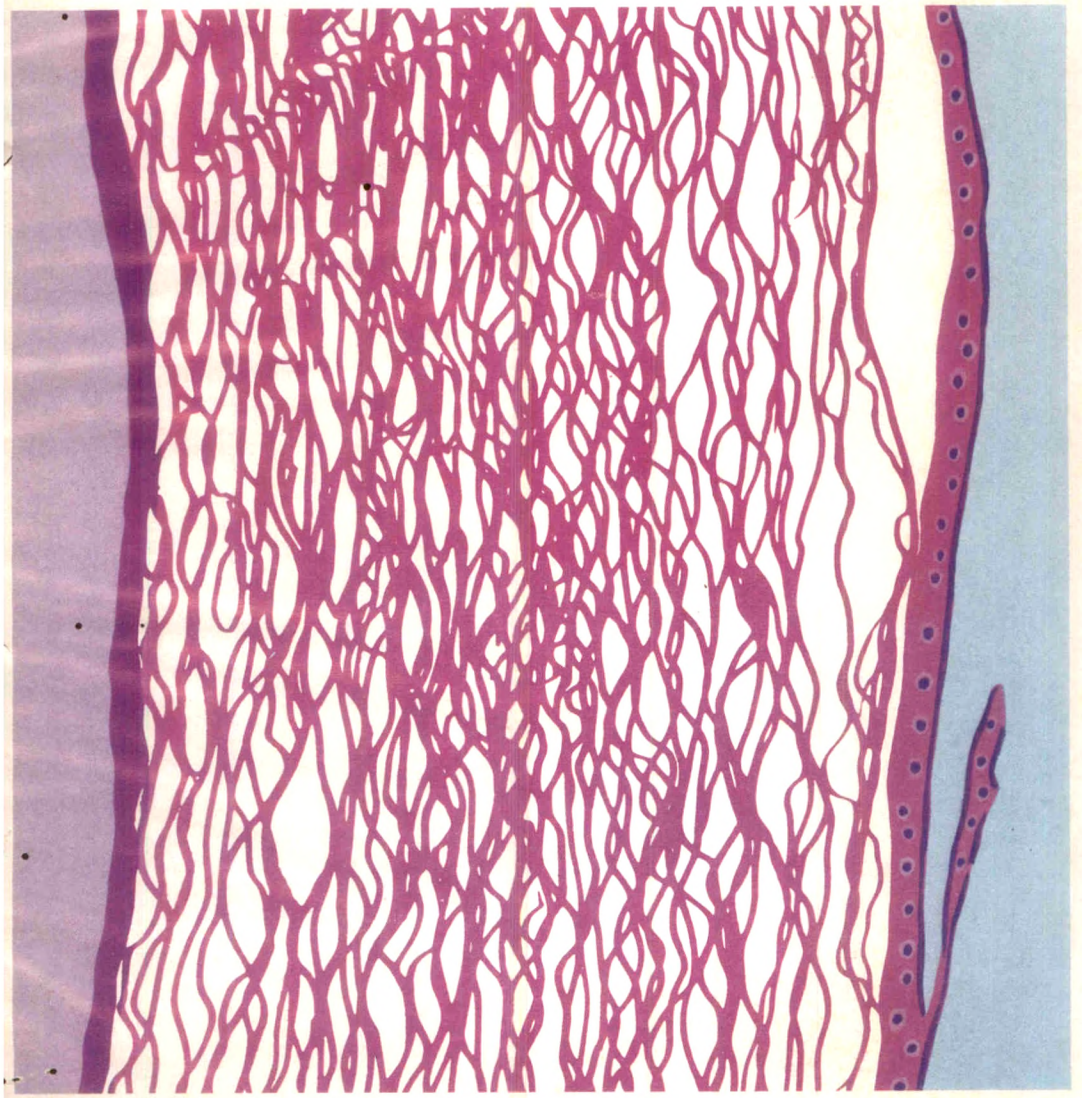
PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on prolonged use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:
1. For glaucoma, the recommended dosage is 1 mist application two to four times a day of the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations should be used.
3. The dosage and strength required to reverse mydriasis depends on the cycloplegic used.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P ***pilocarpine HCl*** ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

Bausch & Lomb

soflens®
(polymacon)
CONTACT LENS

Advances into Ocular Therapy



Bullous Keratopathy

Clinical experience*:
77.3% of patients demonstrate pain relief.

Clinical studies conducted by 21 ophthalmologists in hospitals and private clinical practices confirm SOFLENS® (polymacon) Contact Lens effectiveness in relieving the pain of bullous keratopathy. Of 348 patients, 269 or 77.3% experienced relief from pain following application of the lens. Seventy-nine patients or 22.7% were unsuccessful in wearing the lens. The primary reasons given for lack of success were poor tolerance, discomfort, no change in symptoms, poor visual acuity, or poor fit.

Therapeutic Advances:

Now SOFLENS Contact Lenses are recommended for relief of the painful symptoms of bullous keratopathy. Although all lens series (B, F, J, N, C, and T) may be utilized as transparent barriers to protect the cornea from eyelid friction, the new plano T series is particularly well suited for this therapeutic application.

Because the T lens is large (14.7mm), relatively thin (.18mm), and fits comfortably on most eyes, it should be the lens of first choice.

Therapeutic Advantages:

The SOFLENS Contact Lens is biologically and chemically inert, dimensionally stable, and reliable. These qualities which make the lens a lens of choice in vision correction, when indicated, now provide an effective modality to aid the physician in meeting his therapeutic goals. Placement of the lens generally results in rapid pain relief for the patient.

Therapeutic Convenience:

Medication with preservatives may be used in the usual dosage regimens when indicated. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens. Since all SOFLENS Contact Lens series and powers are available for the treatment of bullous keratopathy, vision correction may also be possible.

SOFLENS Contact Lenses are contraindicated in the presence of any active, untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

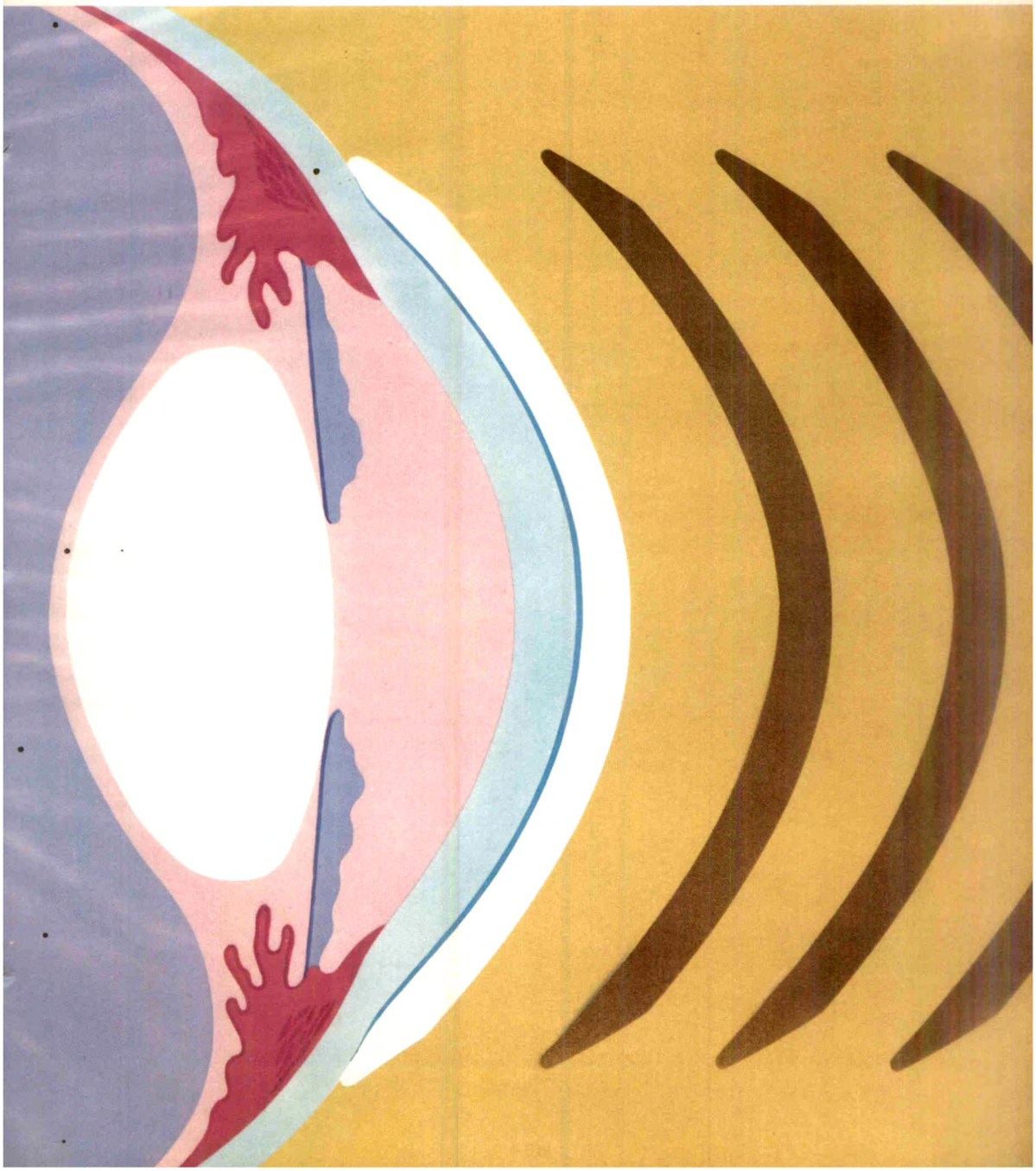
SOFLENS Contact Lenses are easily applied by the physician. Because of flexibility and thin edges of the lenses, most patients adjust to them quickly. While the patient's pain is controlled, the physician gains time to consider other therapeutic procedures. Thus, the SOFLENS Contact Lens preserves future therapeutic options.

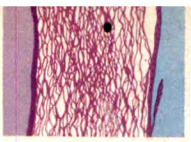
*Data on file at Bausch & Lomb Incorporated. Available on request.

For Bullous Keratopathy you can prescribe with confidence

soflens®
(polymacon)
CONTACT LENS

For therapeutic application, choose the new plano T series or... the B, F, J, N, and C SOFLENS Contact Lens series.





(polymacon) CONTACT LENS

THERAPEUTIC USE

DESCRIPTION: The SOFLENS® (polymacon) Contact Lens is a hemispherical flexible shell which covers the cornea and may cover a portion of the adjacent sclera. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The material has a refractive index of 1.43 and the lens has a visible light transmittance of more than 97%.

ACTIONS: In its hydrated state a SOFLENS Contact Lens is soft and pliable. When placed on the human cornea, the hydrated SOFLENS Contact Lens acts as a refracting medium to compensate spherical ametropias and as a pain reliever by providing a well tolerated barrier between the exposed corneal nerves and the lids.

INDICATIONS: SOFLENS® (polymacon) Contact Lenses may be useful in the treatment and management of painful bullous keratopathy.

CONTRAINDICATIONS: SOFLENS Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

WARNINGS: Patients should be instructed to consult their physician if the eye becomes uncomfortable or irritated. If undue delay is anticipated, the lens should be removed immediately and stored in normal saline.

SOFLENS Contact Lenses must not be used in combination with solutions commonly used for cleaning, wetting and storage of hard contact lenses as these will produce severe corneal irritation.

The patient should be instructed to use only eyedrops prescribed by the physician when the lens is on the eye.

Medication with preservatives may be used when indicated in the usual dosage regimens. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens.

Deposits, which frequently occur on the lens with continuous wear, may cause discomfort and necessitate replacement as often as every two or three months.

SOFLENS® (polymacon) Contact Lenses should not be used in the presence of noxious and irritating vapors. Safety in pregnancy has not been substantiated. Insufficient lacrimal secretion or hypoesthesia may be restricting factors to the wearing of soft contact lenses.

Malfunction and rusting of the metal interior of the Aseptor®–Patient Unit as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure.

Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses.

PRECAUTIONS: Placement and Removal–SOFLENS® (polymacon) Contact Lenses should be applied and removed only by the physician. However, all patients should be instructed in the techniques of placing and removing a lens, so they can do so should it become necessary.

When the SOFLENS Contact Lens is used for the treatment of painful bullous keratopathy, it is to be worn continuously, for 24 hours a day, following the initial application. The patient should be followed closely during the initial stages of treatment. The lens should be comfortable and the pain of bullous keratopathy should be relieved almost immediately. If the lens is not comfortable and pain persists, another lens should be tried for appropriate fit.

Daily placement and removal of the lens by the patient may be permitted. However, if daily removal increases the risk of additional damage to the already compromised corneal epithelium and when the degree of pain relief is significant during the time the lens is worn, continuous wear should be employed.

Storage–SOFLENS® (polymacon) Contact Lenses must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in normal saline solution until it returns to its soft, pliable state which may take as long as forty minutes.

Fresh normal saline must be prepared for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The one ounce squeeze bottle is intended for preparation of normal saline only. As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected.

Hygiene–Hands must be washed, rinsed thoroughly, and dried with a lint-fr towel before handling the lenses.

Cosmetics, lotions, soaps, and creams must not come in contact with the lens since eye irritation may result. If hair spray is used while the lenses are bei worn, the eyes must be kept closed until the hair spray has settled.

Handling–A SOFLENS® (polymacon) Contact Lens may be damaged by nicking tearing if care is not exercised during placement on or removal from the ey replacing or removing it from the carrying case or in the cleaning process. Lens must be placed very carefully in the carrying case to avoid damaging the edges the lenses.

Disinfecting–Fresh normal saline must be prepared daily. After removal from t eye, the SOFLENS® (polymacon) Contact Lens must be irrigated with saline a rubbed gently to remove mucus and film from the lens' surface. The carrying ca must be emptied and refilled with fresh normal saline solution just befo disinfecting the lenses.

The SOFLENS Carrying Case should be washed at least once a week with h water and then rinsed thoroughly with distilled water. Soap or other cleane should never be used to clean the carrying case.

Disinfecting with the SOFLENS Aseptor®–Patient Unit is necessary to k microorganisms.

If a SOFLENS Aseptor is not available, the lenses may be disinfected by boili them in their carrying case in a pan of water for 15 minutes. When this boili method of disinfection is used, the lenses can be damaged if the boiling water allowed to completely evaporate.

The carrying case must always be tightly closed before disinfecting to preve leakage of the saline from the case and subsequent dehydration of the lense

Fluorescein–Never use fluorescein while the patient is wearing the lens because the lenses will become discolored. Whenever fluorescein is used, flu the eyes with sterile normal saline solution and wait at least one hour befo replacing the lenses. Earlier replacement may cause the lenses to absorb residu fluorescein.

ADVERSE REACTIONS: Infiltrates, neovascularization, and corneal ulcers ha been reported.

Serious corneal damage may result from wearing a SOFLENS® (polymaco Contact Lens which has been soaked in a conventional contact lens solution.

Eye irritation may occur within a short time after putting on a hypertonic len Removal of the lens will relieve the irritation.

A lens adheres very rarely to an eye as a result of sleeping with the lens on, wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline a wait until the lens moves freely before removing it.

A faint blue haze, believed to be located in Descemet's membrane, has be reported in the Spokane, Washington area in approximately 26 wearers wi otherwise normal eyes. As yet, the cause is unknown and the phenomenon has n been found elsewhere. The wearers report no subjective symptons and there is detectable effect on their visual acuity.

HOW SUPPLIED: Each lens is supplied sterile in a glass vial containing steri normal saline solution. The glass vial is marked with the manufacturing l number of the lens and the dioptric power (black for plus power lenses; red f minus; gold for plano).

The SOFLENS Care Kit is available for lens disinfecting, cleaning and storag consisting of the following:

SOFLENS Carrying Case	Cat. #140301
SOFLENS Aseptor®–Patient Unit	Cat. #140302
SOFLENS Squeeze Bottle	Cat. #140304
SOFLENS Salt Tablets	Cat. #140305
SOFLENS Patient Instruction Book	Cat. #140300-1

Caution: Federal Law Prohibits Dispensing Without a Prescription

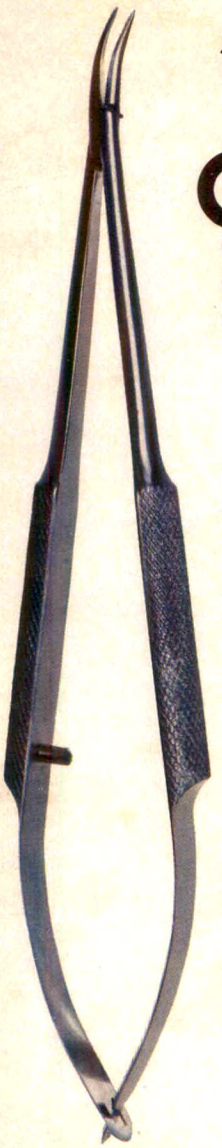
MARCH 1975

BAUSCH & LOMB
SOFLENS DIVISION
Rochester, N.Y. 14602

WECK

introduces

titanium ophthalmic instruments



The first of a "new generation" of ophthalmic instruments.

Discover all of the inherent advantages of titanium alloy with new, unique excellency in instrument designs.

- rounded handles
- stronger
- lighter weight
- low reflectivity

Rounded handles facilitate fingertip rotation, and also specially designed tips, for more natural, precise movements.

Stronger... yet much lighter and more resistant to corrosion than stainless steel . . . with blue finish to minimize glare.

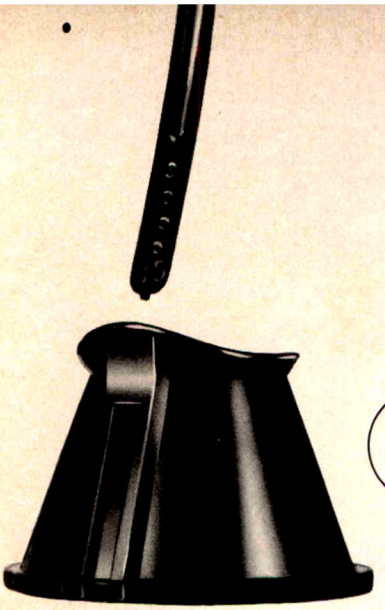
A new line of instruments for intraocular lens implantation is included.

Instrument shown is Tennant Needle Holder #4042 without lock.

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Eisner Scleral Indentation Funnel set





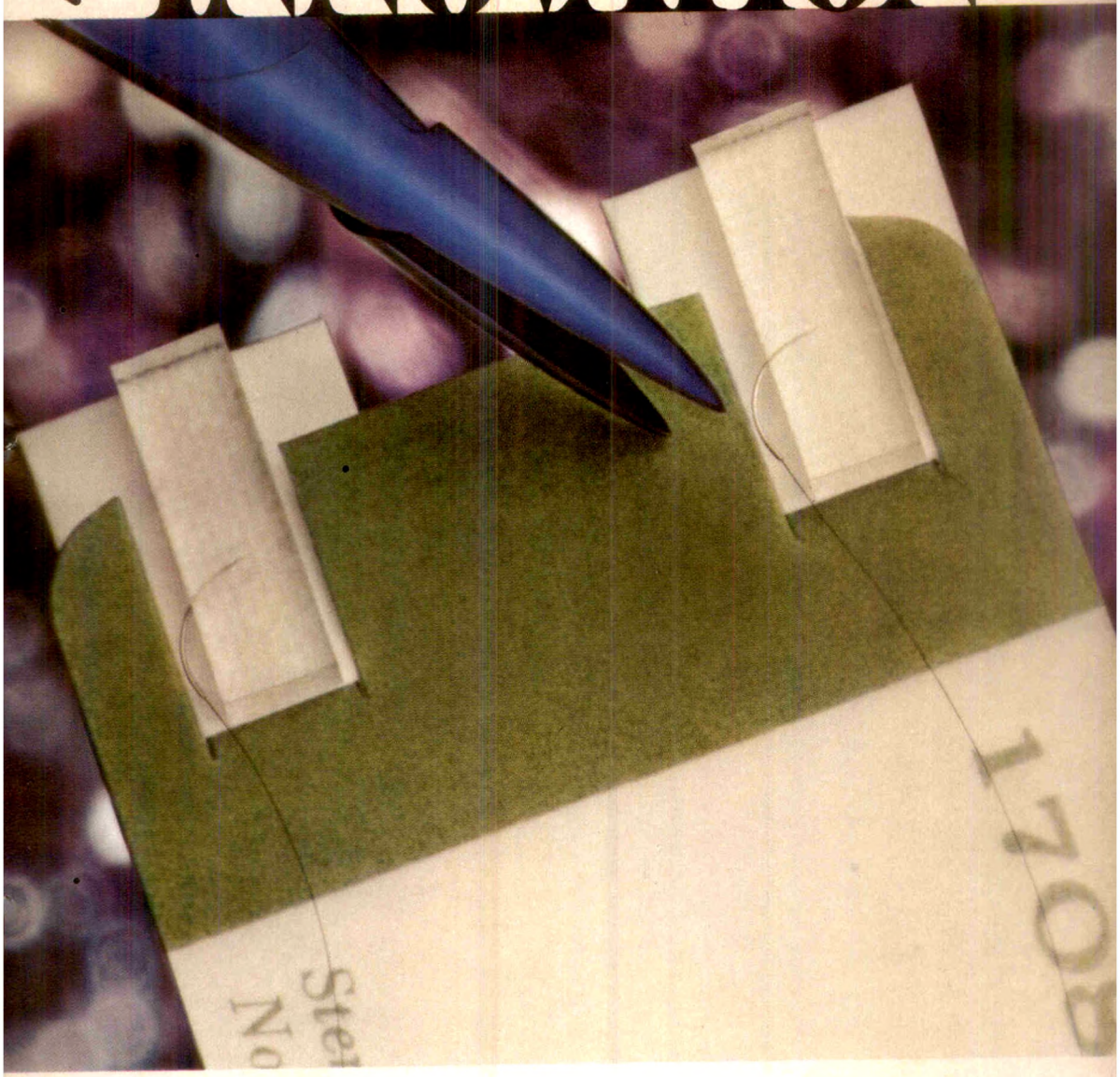
. . . for biomicroscopic examination of the eye with the Goldmann three mirror contact lens. Ideally suited for visualization of the outermost peripheral fundus.

For more information ask your Sparta representative for a demonstration, or request a copy of our illustrated brochure.

Ref. G. Eisner, M.D., "Attachment for Slit-Lamp Contact Glass with Indentor of Variable Length", American Journal of Ophthalmology, 76, (November, 1973), 845.

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INNOVATION



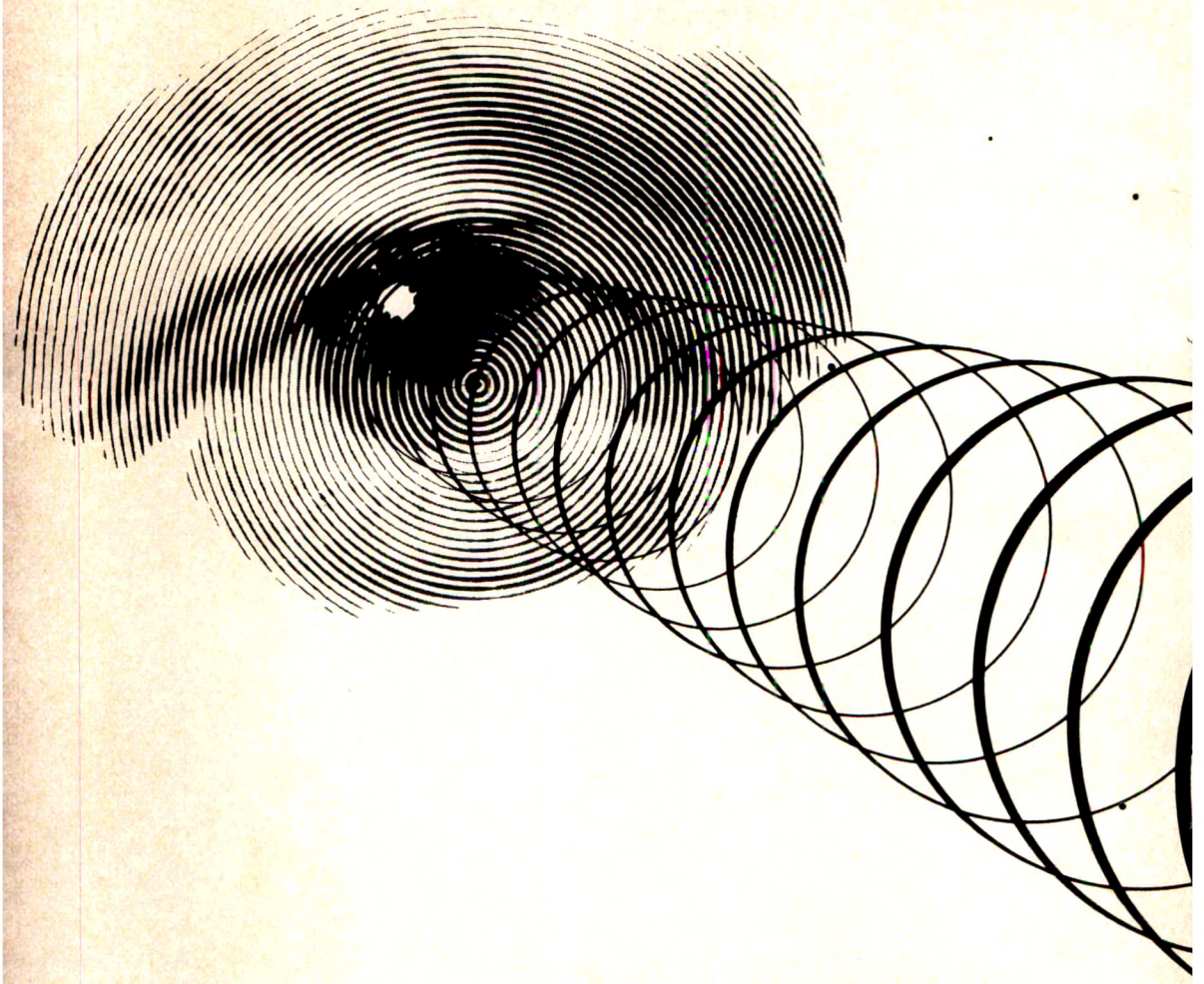
Innovation is in your hands with
ETHICON* needle/sutures for ophthalmic microsurgery.

Most comprehensive line of fine wire
MICRO-POINT* Spatula needles.
Double armed in a new see-through package
with removable needle parks
for ease of delivery.

ETHICON

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For uninterrupted control of I.O.P. ...never more than one or two instillations



Scanning electron microscopy of primate trabecular meshwork (X300):
Viewed here is Schlemm's canal along with uveal and corneoscleral meshwork. (Photo courtesy Douglas R. Anderson, M.D.)

This area is the site of the prime pathologic changes which are responsible for glaucoma and the focus of most of the medical procedures for treatment of the disease.

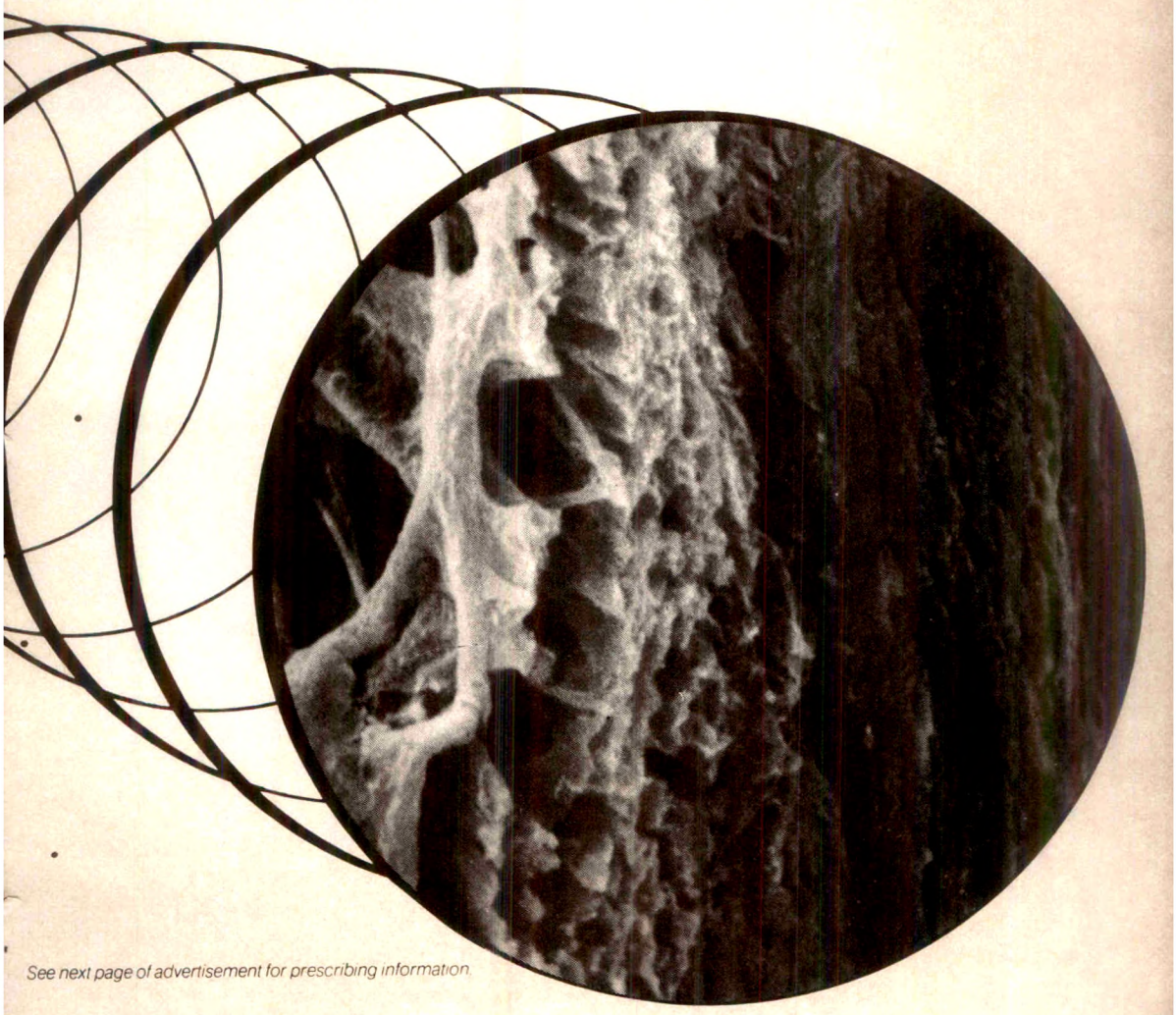
Because PHOSPHOLINE IODIDE is long-acting, it can help provide uninterrupted control of intraocular pressure in chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia. Just one or, at most, two instillations of PHOSPHOLINE IODIDE (one at bedtime, and, if necessary, one in the morning) are generally needed.

Although PHOSPHOLINE IODIDE is longer-acting than other miotics, it is *not* more potent. With four concentrations available, it offers a high degree of dosage flexibility for uninterrupted control of intraocular pressure...used alone or in combination with other medication.

When starting PHOSPHOLINE IODIDE therapy, 0.03%—the lowest strength—is the logical choice. If strengths of 0.06%, 0.125%, or 0.25% are required, the initial use of the 0.03% will be helpful in smoothing the transition.

PHOSPHOLINE IODIDE® not more potent... but longer-acting

(echothiophate iodide for ophthalmic solution)



See next page of advertisement for prescribing information.

PHOSPHOLINE IODIDE®
(echothiophate iodide)
in the management of chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia

BRIEF SUMMARY
(*For full prescribing information, see package circular.*)
PHOSPHOLINE IODIDE® (echothiophate iodide)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia—Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.
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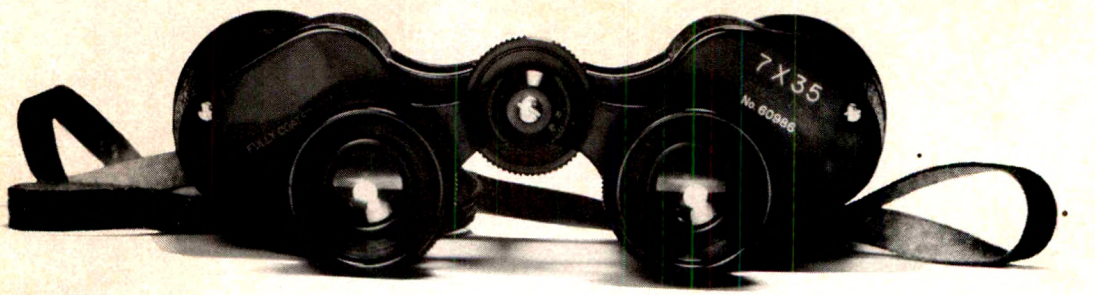
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By David D. Michaels, M.D. October, 1975. Approx. 518 pages, 7″ × 10″, 394 illustrations. About $45.00.

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By J. Donald M. Gass, M.D. 1974, 371 pages plus FM I-X, 8½″ × 11″, 794 illustrations and 112 stereoscopic views in full color on 16 View-Master® reels keyed to labeled drawings and figures, and a View-Master® compact viewer. Price, $72.50.

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Edited by Jared M. Emery, M.D. and David Paton, M.D. December, 1974. 442 pages plus FM I-XX, 7" × 10", 241 illustrations. Price, $39.50.

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Compiled and edited by Joel S. Glaser, M.D. and J. Lawton Smith, M.D. December, 1975. Approx. 312 pages, 6¾" × 9¾", 259 illustrations, 2 in color. About $32.50.

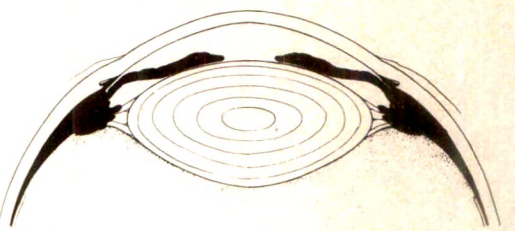
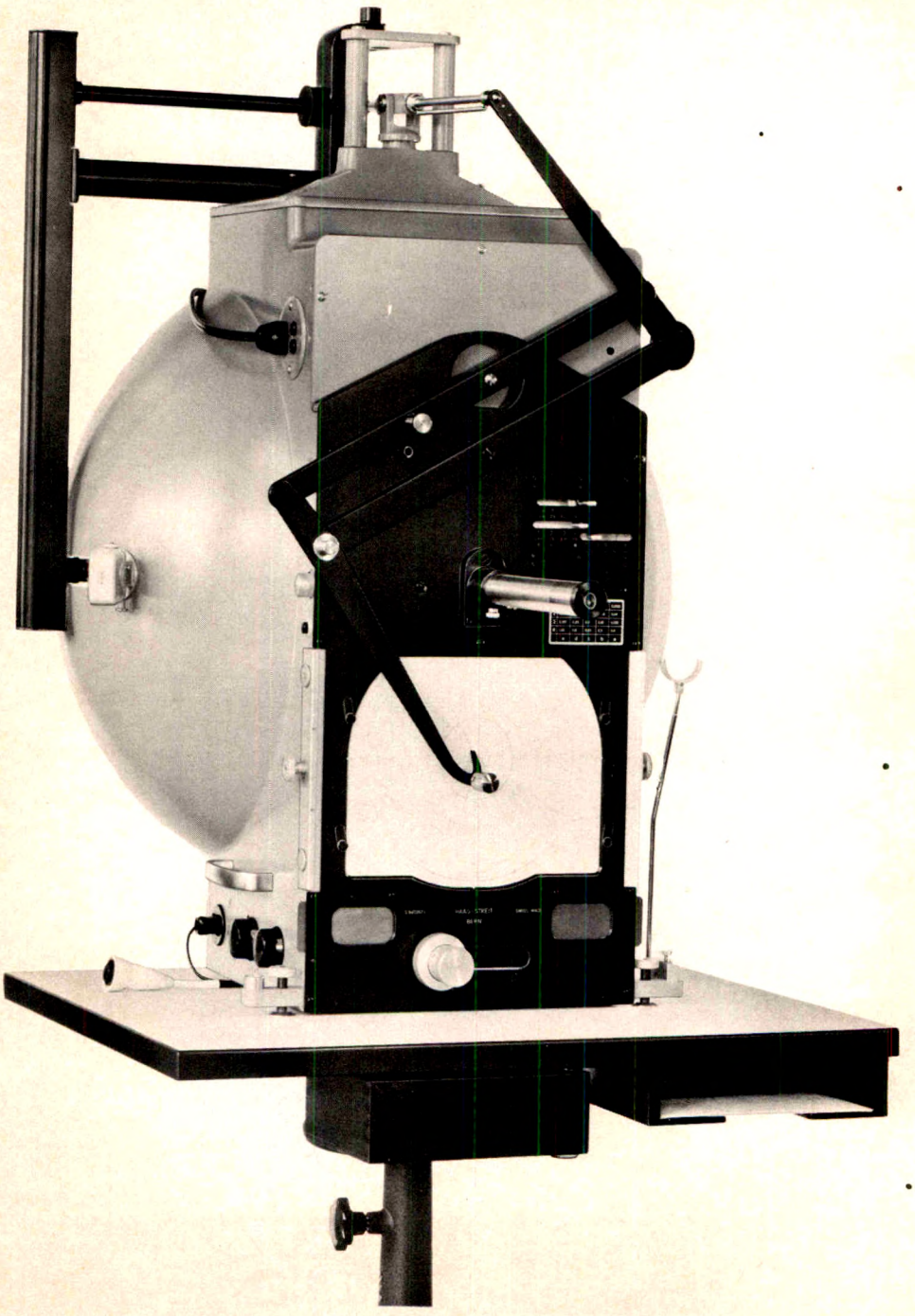


Fig. 22-6. Iridolenticular block, relative pupillary block. (From Shaffer, R.: A suggested anatomic classification to define the pupillary block glaucomas, Invest. Ophthalmol. **12**[7]:540-542, July, 1973.) *(From CURRENT CONCEPTS IN CATARACT SURGERY)*

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Announces a Symposium on

OPHTHALMIC PLASTIC AND CORNEAL SURGERY

To be held at the Doral Beach Hotel
Miami Beach, Florida
April 11-16, 1976

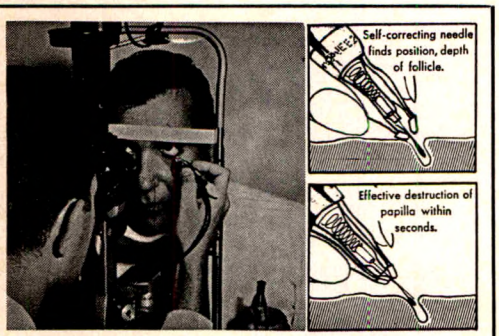
Faculty for the course will include:

Dr. Jorge Buxton
Dr. Henry Clayman
Dr. Robert Dryden
Dr. Richard K. Forster
Dr. Arthur Grove, Jr.
Dr. Norman Jaffe
Dr. Richard Keates
Dr. Peter Laibson
Dr. James Major
Dr. Gordon Miller
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Dr. Byron Smith
Dr. Richard Tenzel
Dr. Ira Weiner
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This symposium will cover the corneal and ophthalmic plastic field. Multiple lectures will be given with ample time for panel discussion and questions from the registrants.

Afternoons will be set aside for recreation including tennis and golf tournaments. There will be planned entertainment for most evenings.

Tuition will be $250, breakfast included. Special rate of $125 available for residents upon application from their Department Head. Checks should be made payable to "Bascom Palmer Eye Institute" and mailed to Ophthalmic Plastic Surgery Symposium, Bascom Palmer Eye Institute, P.O. Box 520875, Biscayne Annex, Miami, Florida 33152.



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brand of
gentamicin sulfate, U.S.P.
OPHTHALMIC
Solution-Sterile
Ointment-Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci; and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species, including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

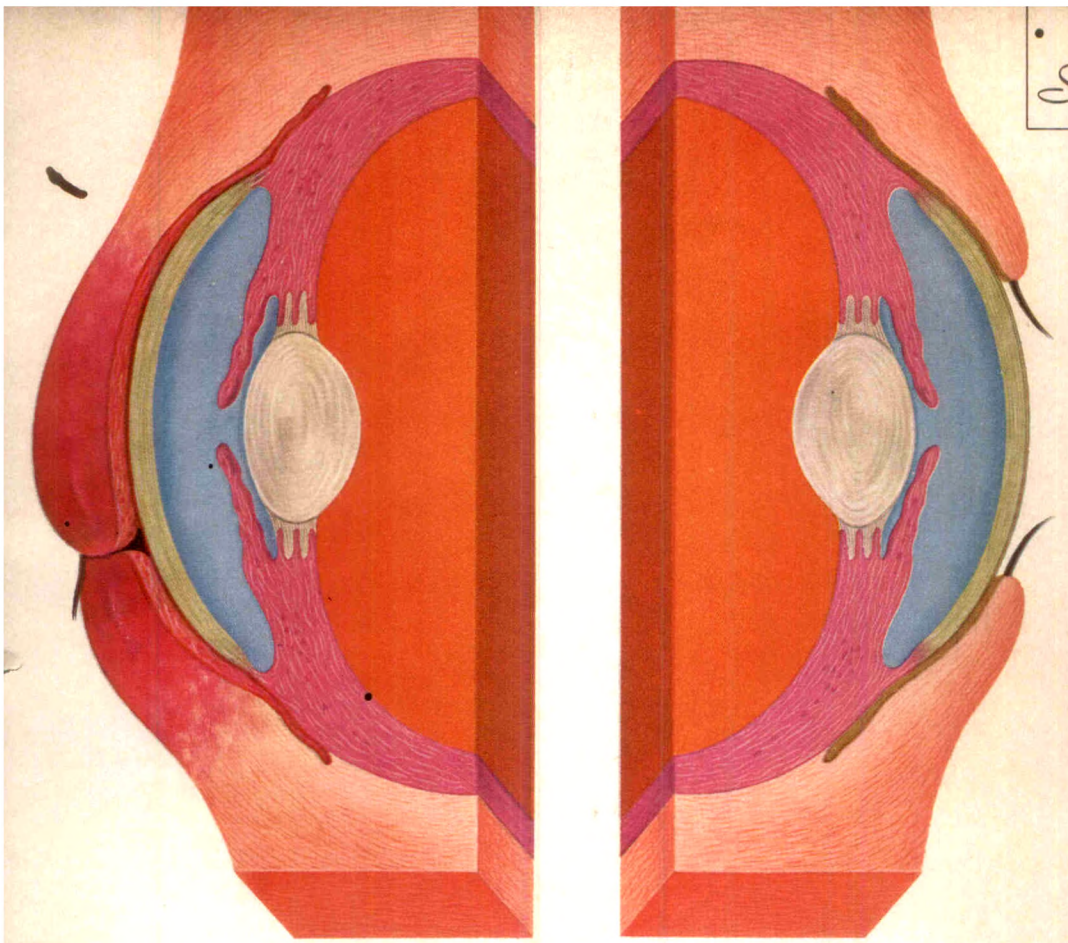
HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube, boxes of one and six. Store away from heat.

NOVEMBER 1973

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■ Clears up conjunctivitis and other infections of the external eye and adnexa due to susceptible strains of gram-negative *H. influenzae, E. coli, K. pneumoniae, M. lacunata, Enterobacter aerogenes* (formerly *Aerobacter*), *H. aegyptius* and *Neisseria* sp., including *N. gonorrhoeae.*

■ Clears up conjunctivitis and other infections of the external eye and adnexa due to susceptible strains of gram-positive staphylococci and streptococci, including *D. pneumoniae*.

■ Clears up infections* of the external eye and adnexa due to problem organisms: *P. aeruginosa* (certain strains) and *Proteus* sp. (sensitive strains, both indole-positive and -negative).

■ Clears up infections* of the external eye and adnexa generally without sensitivity reactions and irritation. No significant organism resistance to date. This may occur in the future. Resistance to gentamicin has been produced (with difficulty) *in vitro* by repeated exposures.

Clears up external eye infections* caused by a wide range of ocular pathogens

*due to susceptible organisms.

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brand of gentamicin sulfate, U.S.P.

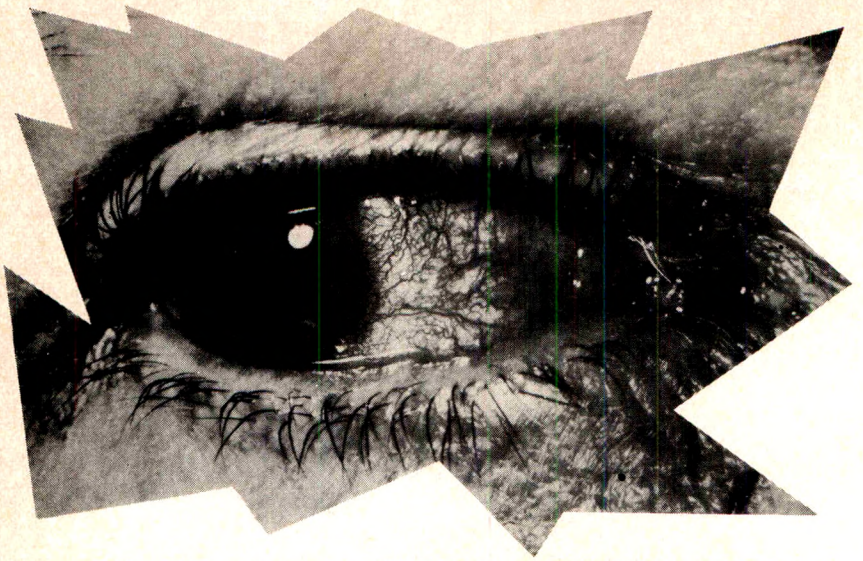
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Solution-Sterile
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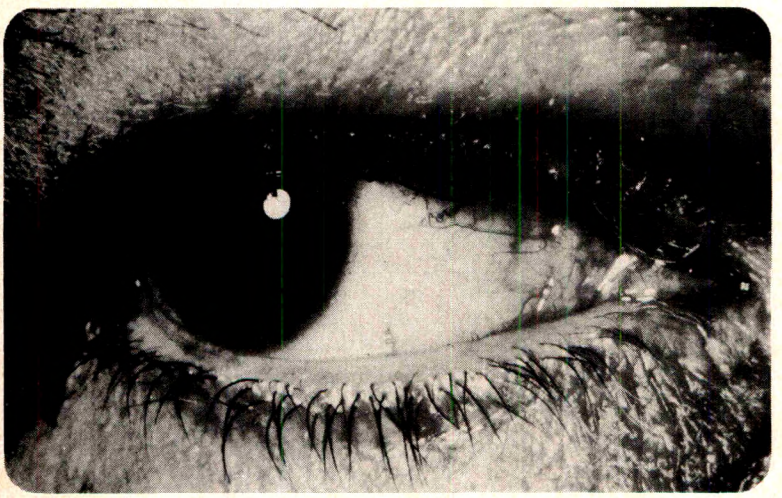
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Solution: NEOSPORIN® Ophthalmic Solution sterile

(polymyxin B-neomycin-gramicidin)



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Polymyxin B-Neomycin-Gramicidin

CONTRAINDICATIONS:
This product is contraindicated in those persons who have shown sensitivity to any of its components.

WARNINGS:
Prolonged use may result in overgrowth of nonsusceptible organisms.

PRECAUTIONS:
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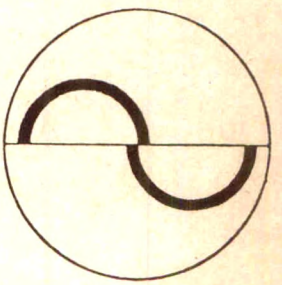
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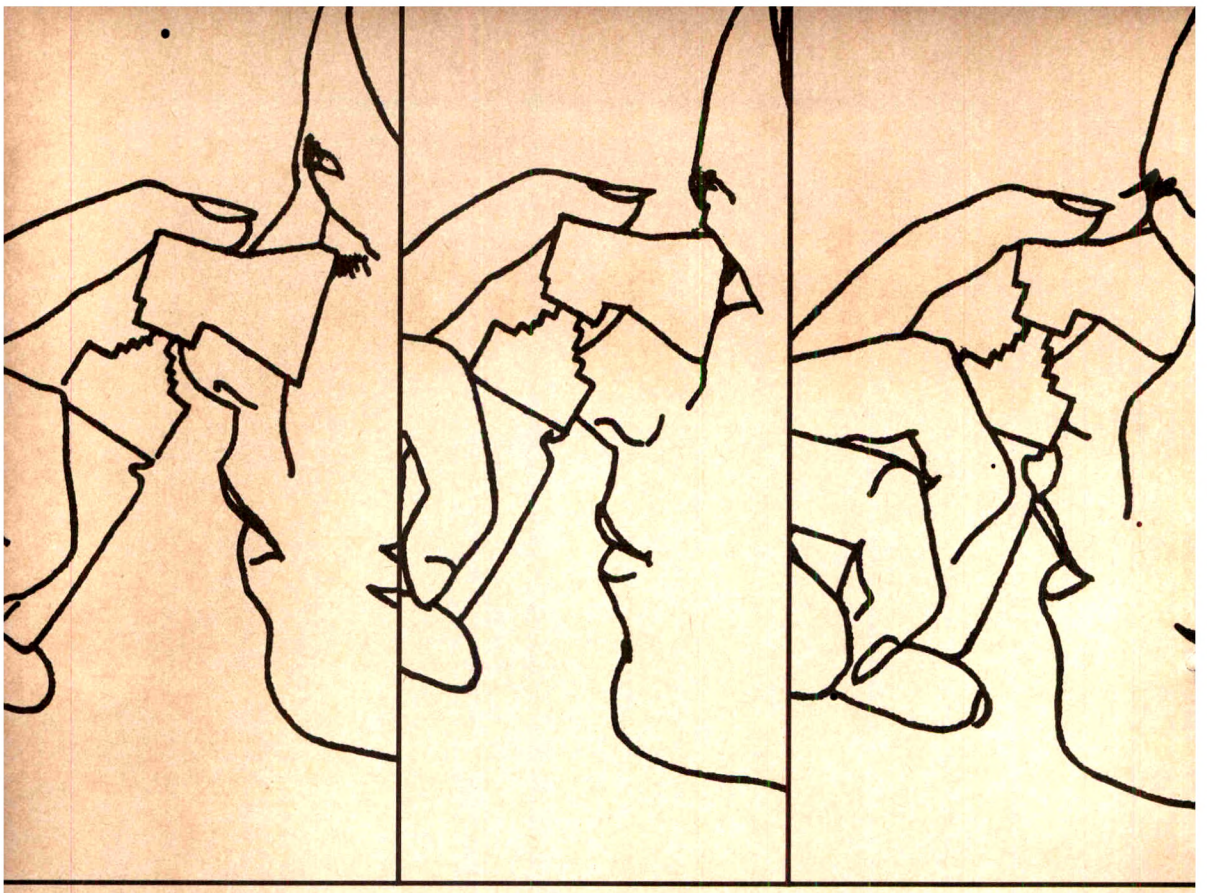
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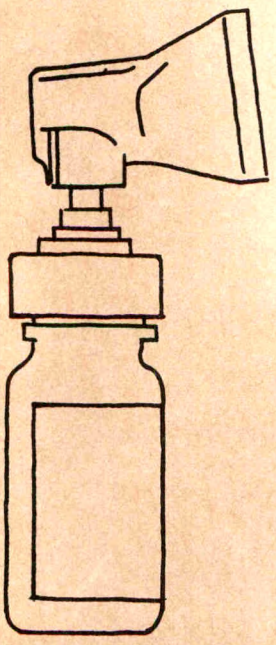
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Hold MISTURA between index finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone. Look up within the eye-scope.

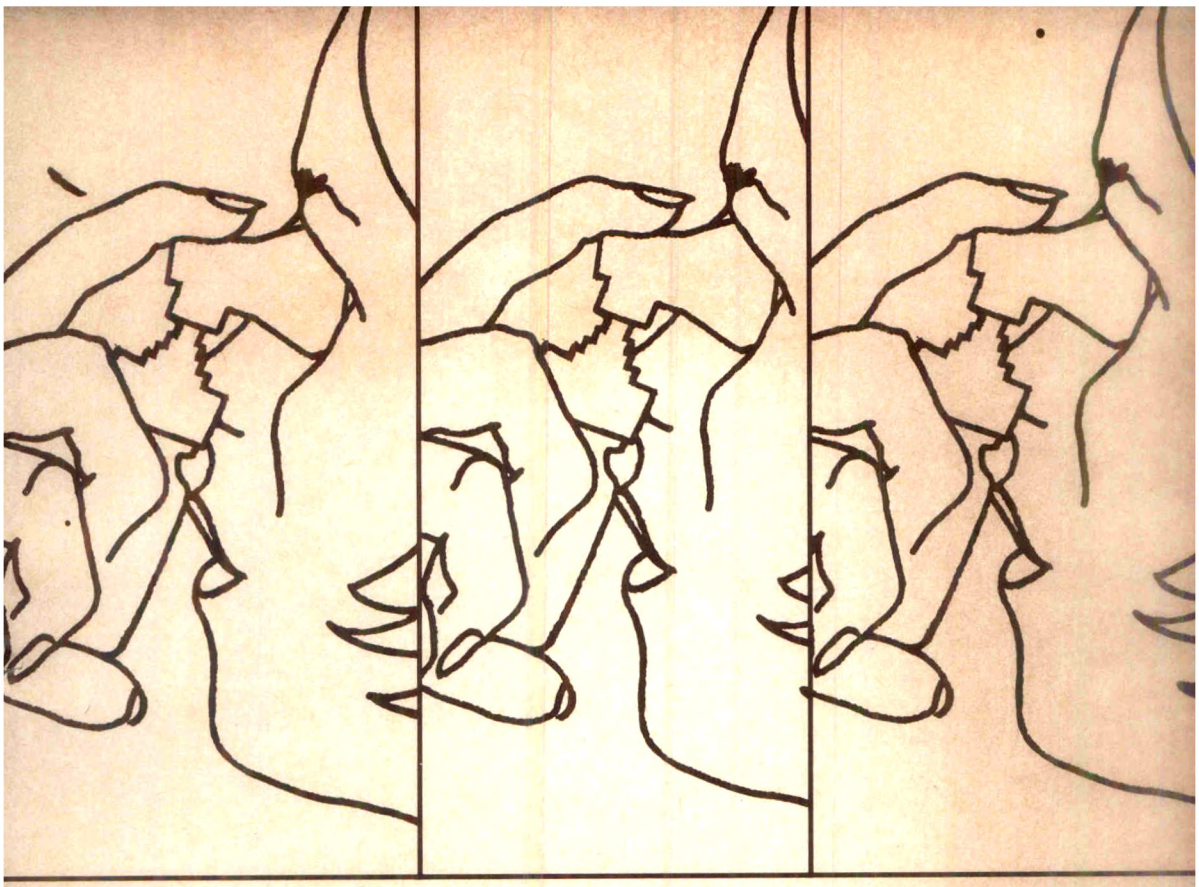
Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.



Used properly, MISTURA can assure complete coverage of the absorbing surface of the eye for effective I.O.P. control.

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Ophthalmic Spray Products



The longer they use it the better they like it.

168 dropper users tried MISTURA. 71% like it.* 28 opthalmologists recently switched from dropper medication with pilocarpine to MISTURA® P Pilocarpine HCl. Acceptance increased with use. At the end of the first week, 63% liked it—by the second week, patient acceptance increased to 71%. Typical comments included:

"It's more convenient." "I don't have to tip my head." "Less trouble keeping my eyes open." "I can do it myself, my wife had to help me before." Is MISTURA a better way to deliver a drop? Most patients who try it think so!

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Please see prescribing information on last page of this advertisement.

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev.7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with: benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E */-epinephrine* to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for the difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES

1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 as a preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P *pilocarpine HCl* is indicated for:

1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on prolonged use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:

1. For glaucoma, the recommended dosage is 1 mist application two to four times a day of the selected concentration; patient response may be variable.

2. To aid in emergency miosis, 1 mist application of the higher concentrations should be used.

3. The dosage and strength required to reverse mydriasis depends on the cycloplegic used.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

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CRYOEXTRACTOR FROM ALCON

EXTRA ENGINEERING PUTS IT IN A CLASS BY ITSELF

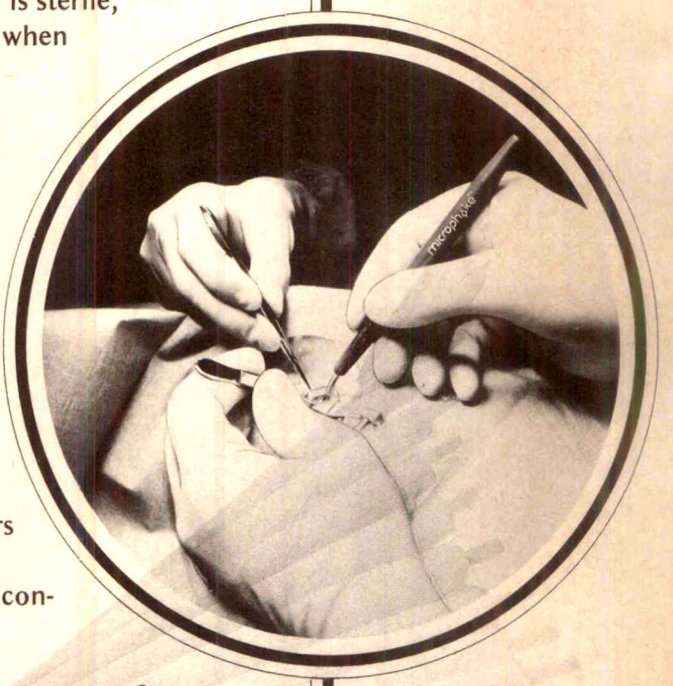
MICROPHAKE cryoextractor is sterile, self-contained. . .ready to use when you need it.

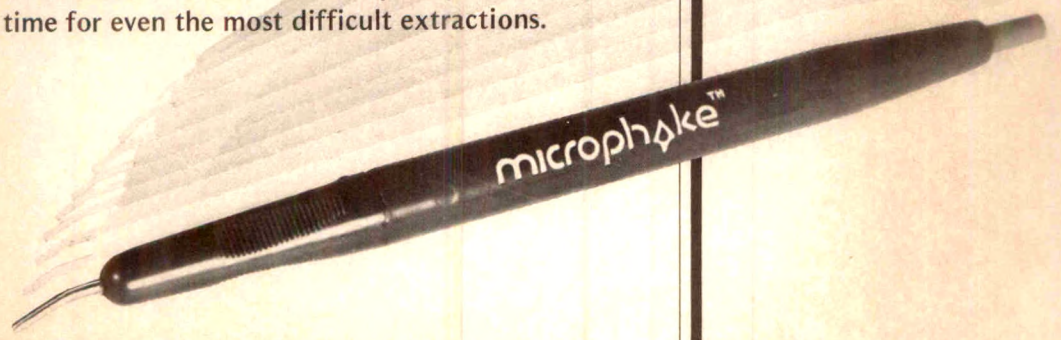
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MIDWINTER CONTACT AND CONTACT LENS ASSOCIATION

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SAHARA HOTEL, LAS VEGAS, NEVADA

OLIVER H. DABEZIES, JR., M.D.
CHAIRMAN

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EIGHTH CONRAD BERENS MEMORIAL LECTURE
WHITNEY G. SAMPSON, M.D., Houston, Texas
"THE CURRENT STATUS OF MEDICAL CONTACT LENS PRACTICE"

DISTINGUISHED VISITING LECTURER
JOHN F. MORGAN, M.D., F.R.C.S. (C), Kingston, Ontario, Canada

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INTRAOCULAR LENS MEETING
OF OPHTHALMOLOGISTS, INC.

(Registration will start Thursday, January 29, 1976, 5-9 p.m.
Meeting will start Friday at 9:00 a.m. and will end Sunday at 1:00 p.m.)

G. PETER HALBERG, M.D., F.A.C.S.
SECRETARY

COURSES

Course No. 1
Elementary Hard and Soft Contact Lens Fittings
Course Director: G. Peter Halberg, M. D.
Instructors: To Be Announced

Course No. 2
Therapeutic Lenses and Scleral Shells
Course Director: Herbert L. Gould, M.D.
Instructors: John W. Espy, M.D., Marsha Guibor

Course No. 3
Conventional Corneal Lenses: Fitting Principles and Problem Management
Course Director: Perry Rosenthal, M.D.
Instructors: To Be Announced

Course No. 4
Soft Contact Lens Fitting with Custom Designed Lenses
Course Director: Paul R. Honan, M.D.
Instructor: Herschell H. Boyd, M.D.

Course No. 5
Bifocal and Unifocal Contact
Lenses for the Presbyope
Course Director: Abraham Schlossman, M.D.
Instructors: Charles E. Clevenger, M.D., George H. Jones, M.D., George B. Pugh, M.D., Carolyn Schlossman, Norman Schmid, Sr., Frank Weinstock

Course No. 6
Therapeutic Hydrophilic Soft Lenses
Course Director: James V. Aquavella, M.D.
Instructors: Joseph A. Baldone, M.D., S. Arthur Boruchoff, M.D., John W. Espy, M.D., Richard H. Keates, M.D., Anthony B. Nesburn, M.D.

Course No. 7
Technological Aspects of Hard and Soft Contact Lenses (Basic Course—Instrumentation, Basic Lens Design, Modification and Follow-up Visits)
Course Director: Joseph Soper
Instructors: Frank Sanning, Kenneth Swanson, Ralph Sutton

Course No. 8
Aphakia—Lens Choice and Management
Course Director: Robert J. Crossen, M.D.
Instructors: Thomas R. Mazzocco, M.D., Robert C. Welsh, M.D.

Course No. 9
Clinical Aspects of Fitting the HydroCurve^{tm} Lens
Course Director: James S. Russell, M.D.
Instructor: Susan Savage

Course No. 10
Cosmetic Fitting with the Bausch & Lomb Soflens
Course Directors: Ellis Gruber, M.D. and Charles O. Titus, M.D.
Instructors: To Be Announced

Course No. 11
Present Status of Silicone Lenses
Course Director: Chester J. Black, M.D.
Instructors: To Be Announced

Course No. 12
Hard and Soft Lenses in the Treatment of Ocular Pathology
Course Director: Frank B. Hoefle, M.D.
Instructors: Jorge N. Buxton, M.D., James Koverman

Course No. 13
Hard Contact Lenses
Course Director: Herschell H. Boyd, M.D.
Instructor: Paul R. Honan, M.D.

Course No. 14
Basics of Hydrophilic Lens Fitting—A Canadian Approach
Course Director: John F. Morgan, M.D.
Instructors: Ronald E. Groshaw, M.D., Bernard J. Slatt, M.D., Harold A. Stein, M.D., John D. Valberg, M.D.

Course No. 15
Orthokeratology
Course Director: Donald A. Fonda, M.D.
Instructors: Richard S. Fixott, M.D.

Course No. 16
The Use of Therapeutic Soft Contact Lenses
Course Director: Robert G. Webster, Jr., M.D.
Instructors: Walter J. Stark, M.D., H. Lee Stewart, M.D.

Course No. 17
Intraocular Lens Surgery, Indications and Contra-indications, Surgical Techniques
Course Directors: Jack Hartstein, M.D. and Richard P. Kratz, M.D.
Instructor: Herbert L. Gould, M.D.

Course No. 18
Surgical Aspects of Contact Lens Patients
Course Director: Pierre Guibor, M.D.
Instructors: Robert A. D'Amico, M.D., Marsha Guibor, Richard C. Troutman, M.D.

Course No. 19
Basic Fitting Technique and Workshop with the Warner-Lambert Softcon Lens
Course Director: Edward Shaw, M.D.
Instructors: To Be Announced

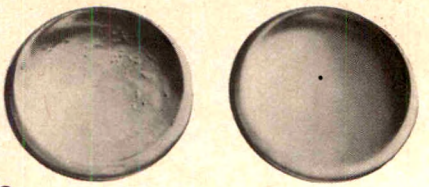
Course No. 20
Aphakic Correction
Course Director: Robert C. Welsh, M.D.
Instructors: Robert J. Crossen, M.D., Herbert L. Gould, M.D., Thomas R. Mazzocco, M.D., Charles Moore

INTRAOCULAR LENS COURSES, Sunday, February 1, 1976, 7-9 A.M.

Six intraocular lens courses will be given. The intraocular lens courses are so arranged that they will not conflict with the remainder of the courses.

Intraocular Lens Course Instructors are: James V. Aquavella, M.D., Stanley C. Becker, M.D., Jorge N. Buxton, M.D., Herve M. Byron, M.D., Robert C. Drews, M.D., Jack Hartstein, M.D., Francis C. Hertzog, Jr., M.D., Kenneth J. Hoffer, M.D., Herbert E. Kaufman, M.D., Richard H. Keates, M.D., Richard P. Kratz, M.D., David M. Worthen, M.D.

Nothing else can clean a soft lens like PLIAGEL.





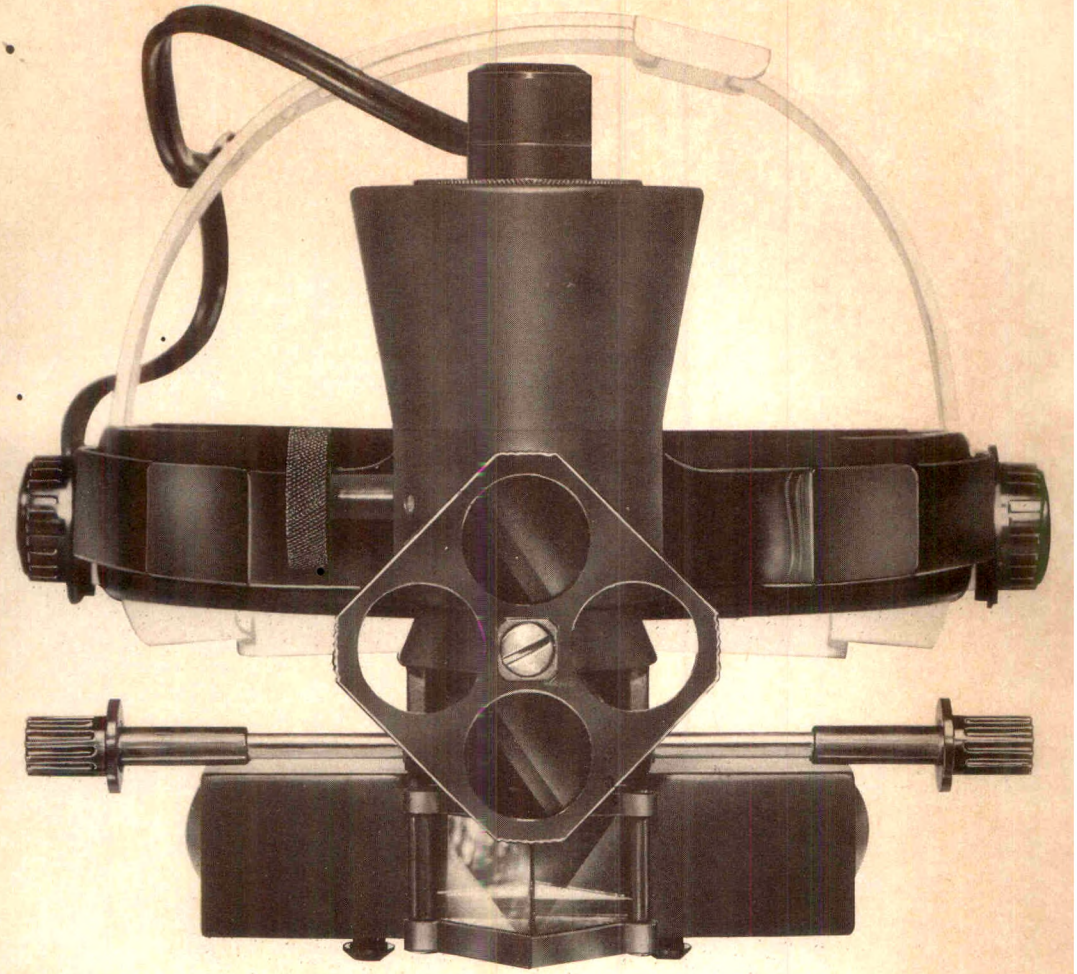
PLIAGEL* Soft Contact lens cleaner for the HydroCurve™ (hefilcon A) Contact Lens PHP.**

- The detergent (Poloxamer 407) concentration in Pliagel is 60 times that in any other soft contact lens cleaner available.
- 15% Poloxamer 407 contained in Pliagel is a good solvent for oils, proteins and other debris found on soft lenses.
- Prophylactic Pliagel cleaning is purely a surface cleaning action.
- The molecular weight of Poloxamer 407 (15,000) is many times greater than the molecular weight of the detergent used in any other cleaner. Poloxamer 407 does not penetrate the lens. It does not produce any lingering discomfort upon lens insertion.
- Poloxamer 407 provides lubricity and cleaning without potential lens scratching and without artificial viscosity-building agents like hydroxyethylcellulose.

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The Fison Indirect Ophthalmoscope bears close examination.

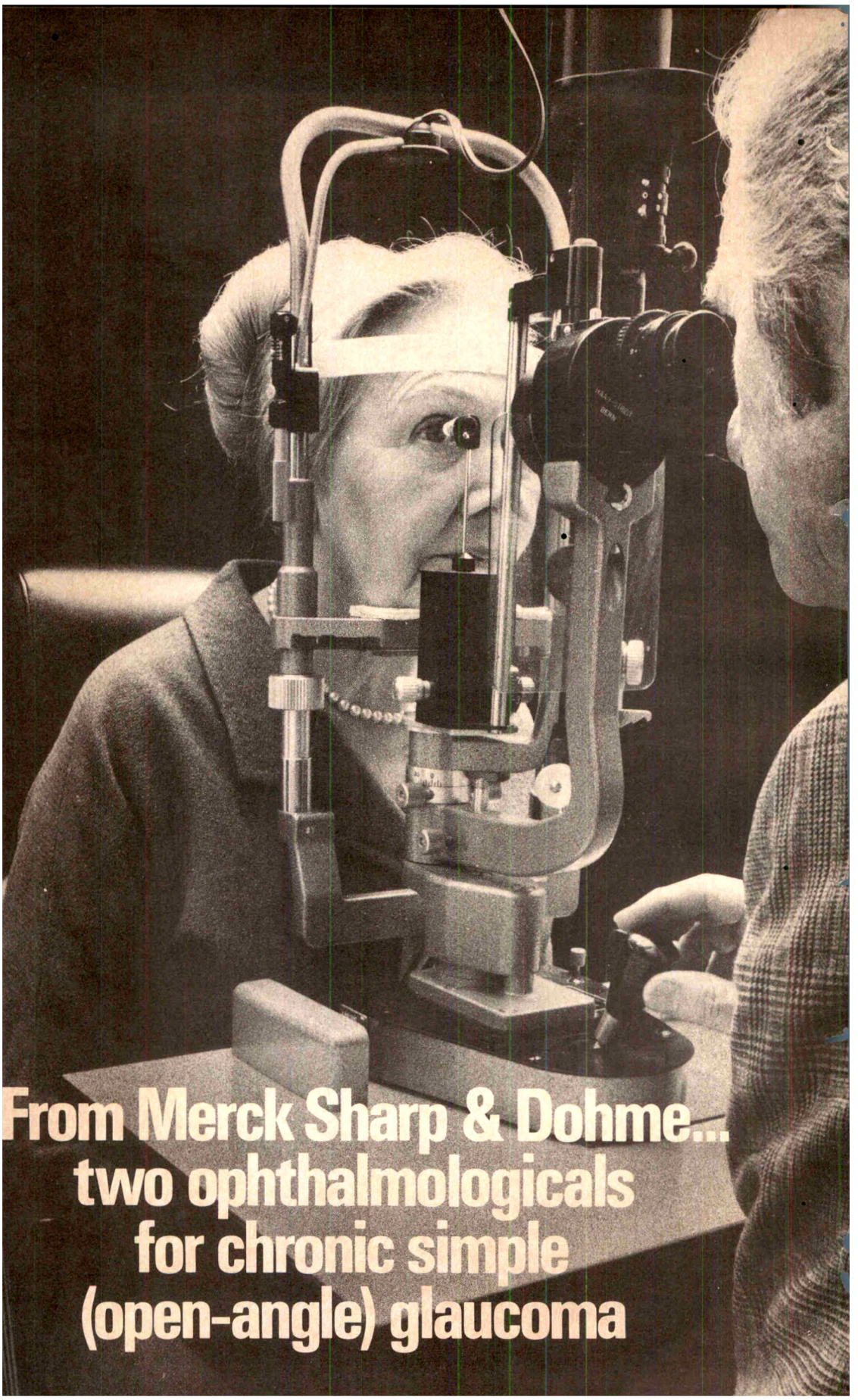
More than an ophthalmoscope, the Fison Indirect was designed as a complete examination system—for diagnosis, teaching and surgery. Many features usually considered as extras are offered as standard with the Fison. And although these accessories are detachable, they are engineered as integral parts of the instrument . . . and need never be removed.

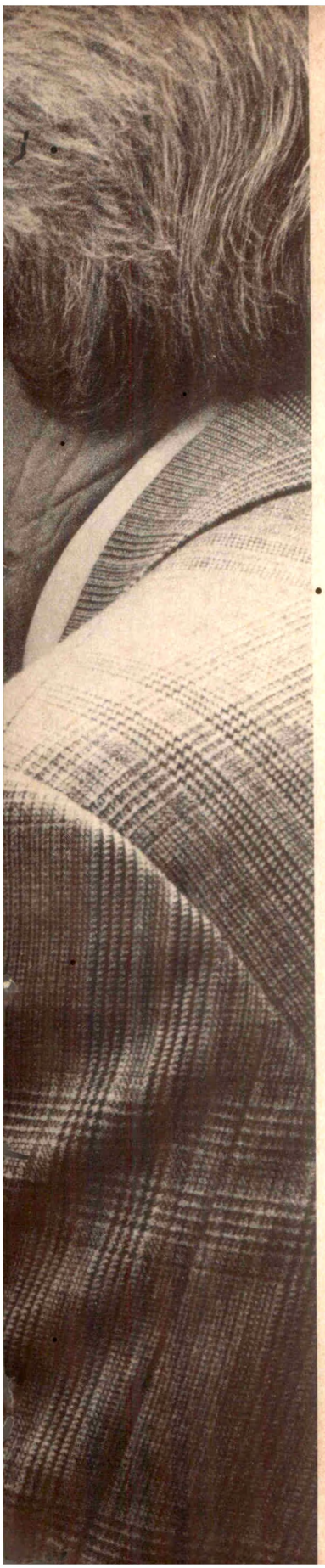
Lightest, most comfortable indirect on the market. • Maximum heat dissipation through cooling cowl. • Convenient filter wheel fitted with interference red-free and blue filters. • Optional yellow eye pieces. • Unique, hinged bi-mirror teaching attachment allows viewing by two additional observers simultaneously. • Stereoscopic view and pre-focused bulb for extremely bright, clear 3D image of fundus. • Instrument and attachments available individually or as complete package.

Examine the Fison Indirect Ophthalmoscope. It should change your point of view.

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When a highly potent long-acting miotic is needed...

OPHTHALMIC SOLUTION, 0.125% and 0.25%

HUMORSOL®

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- Needs no refrigeration
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HUMORSOL is contraindicated in patients with known hypersensitivity to the drug, in active uveal inflammation, and in most cases of narrow-angle glaucoma.

When baseline miotics aren't enough...

TABLETS, 50 mg

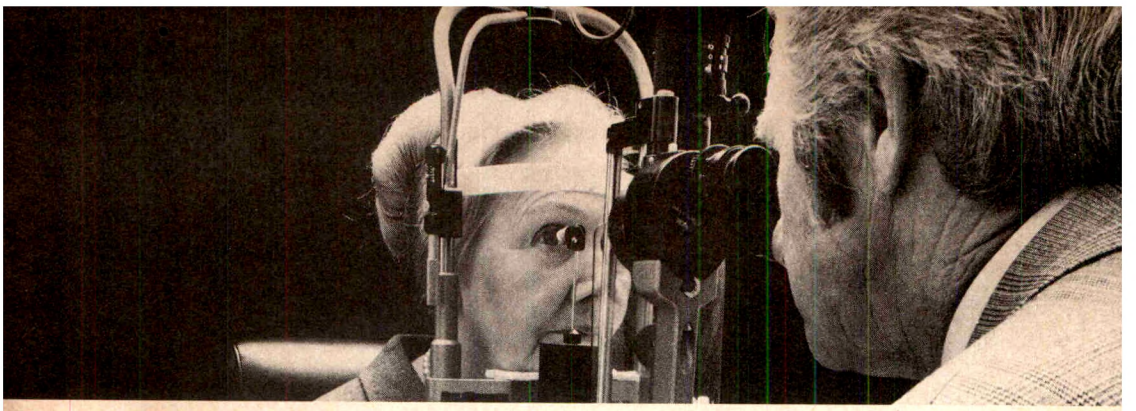
DARANIDE®

(DICHLORPHENAMIDE | MSD)

- Oral carbonic anhydrase inhibitor
- Partially suppresses secretion of aqueous humor
- Best used as adjunct to miotics
- Onset of action usually within an hour; maximal effect is observed in 2 to 4 hours
- Lowered intraocular pressure may be maintained for 6 to 12 hours

DARANIDE is contraindicated in hepatic insufficiency, renal failure, adrenocortical insufficiency, hyperchloremic acidosis, or in conditions in which serum levels of sodium or potassium are depressed. It should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased.

For brief summaries of prescribing information on DARANIDE and HUMORSOL, please see following page.



OPHTHALMIC SOLUTION, 0.125% and 0.25%

HUMORSOL®

(DEMECARIUM BROMIDE | MSD)

FOR TOPICAL APPLICATION INTO THE CONJUNCTIVAL SAC ONLY

Contraindications: Known hypersensitivity; active uveal inflammation; most cases of narrow-angle glaucoma.

Warnings: Should be administered with extreme caution to patients with myasthenia gravis who are on systemic anticholinesterase therapy; conversely, systemic anticholinesterase drugs for myasthenia gravis should be added cautiously. Succinylcholine should be administered with extreme caution before or during general anesthesia, because of possible respiratory and cardiovascular collapse.

Use in Pregnancy: Safe use in pregnancy has not been established, nor has the absence of adverse effects on the fetus or on respiration of the neonate. During pregnancy weigh potential benefits against possible hazards.

Precautions: Gonioscopy is recommended before therapy. Do not use, or use cautiously, when an intraocular inflammatory process is present.

Compression of the lacrimal sac during and following instillation for a minute or two minimizes drainage into the nasal chamber. Wash hands immediately after instillation. Discontinue use if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, or cardiac irregularities occur.

Persons exposed to organophosphate-type insecticides and pesticides (gardeners, organophosphate-manufacturing plant or warehouse workers, farmers, residents of communities which are undergoing insecticide spraying or dusting, etc.) should be warned of added systemic effects possible from absorption through the respiratory tract or skin. Wearing of respiratory masks, frequent washing, and clothing changes may be advisable.

Use with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects. Use extreme caution before intraocular surgery because of the possibility of hyphema.

Despite observance of all precautions, repeated administration may cause depression of the concentration of cholinesterase in the serum and erythrocytes, with resultant systemic effects.

Adverse Reactions: Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, brow ache, headache, and induced myopia with visual blurring; activation of latent iritis or uveitis; retinal detachment has been reported occasionally. Iris cysts may form, enlarge, and obscure vision, more frequently in children; cysts usually shrink when the miotic is discontinued but, rarely, may rupture or break free into the aqueous. Frequent examination is advisable.

Prolonged use may cause conjunctival thickening and obstruction of nasolacrimal canals. If systemic effects occur (e.g., salivation, urinary incontinence, nausea, abdominal cramps, vomiting, diarrhea, dyspnea, bradycardia, cardiac irregularities), parenteral administration of atropine is indicated: 0.4 to 0.6 mg or more for adults, proportionately less for children; artificial respiration may be required. S therapy is indicated for overdosage.

Lens opacities have been reported, and routine sli examinations should accompany prolonged use. Parad increase in intraocular pressure may occur and be alle by a mydriatic.

Dosage and Administration: Initial titration and dosa justments must be individualized to obtain maximal the tic effect. Patient must be observed closely during period. If response is not adequate within first 24 consider other measures. Keep frequency of use to a mum in all patients, but especially in children.

Since technic is crucial to proper and safe administr consult prescribing information for full details.

Supplied: In 5-ml OCUMETER® Ophthalmic Dispenser taining 0.125 or 0.25 percent solution and sodium chl benzalkonium chloride 1:5000 added as preservative.

For more detailed information, consult your MSD represen or see full prescribing information. Merck Sharp & Dohme, Di of Merck & Co., Inc., West Point, Pa. 19486

TABLETS, 50 mg

DARANIDE®

(DICHLORPHENAMIDE | MSD)

Contraindications: Hepatic insufficiency, renal failure, ac cortical insufficiency, hyperchloremic acidosis, or cond in which serum levels of sodium or potassium are depre Should not be used in patients with severe pulmonary ob tion who are unable to increase their alveolar venti since their acidosis may be increased.

Warning: *Use in pregnancy:* Should not be used in wom childbearing age or in pregnancy, especially during the trimester, unless the benefits to be expected outweig tential adverse effects.

Precautions: Potassium excretion is increased and hypo mia may develop with brisk diuresis, when severe cirrho present, or during concomitant use of steroids or A Interference with adequate oral electrolyte intake will contribute to hypokalemia. Hypokalemia can sensiti exaggerate the response of the heart to the toxic effe digitalis. Hypokalemia may be avoided or treated by u potassium chloride or giving foods with a high potas content. Use with caution in severe respiratory acidosis

Adverse Reactions: Side effects (characteristic of car anhydrase inhibitors) may include gastrointestinal dis ances (anorexia, nausea, vomiting), loss of weight, con tion, urinary frequency, renal colic, renal calculi, mild eruptions, pruritus, leukopenia, agranulocytosis, thrombo penia, headache, weakness, nervousness, globus hyste sedation, lassitude, depression, confusion, disorient dizziness, ataxia, tremor, tinnitus, and paresthesias of h feet, and tongue.

How Supplied: Tablets containing 50 mg dichlorphena each, in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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Topcon Advances Projection Perimetry Another Important Step.

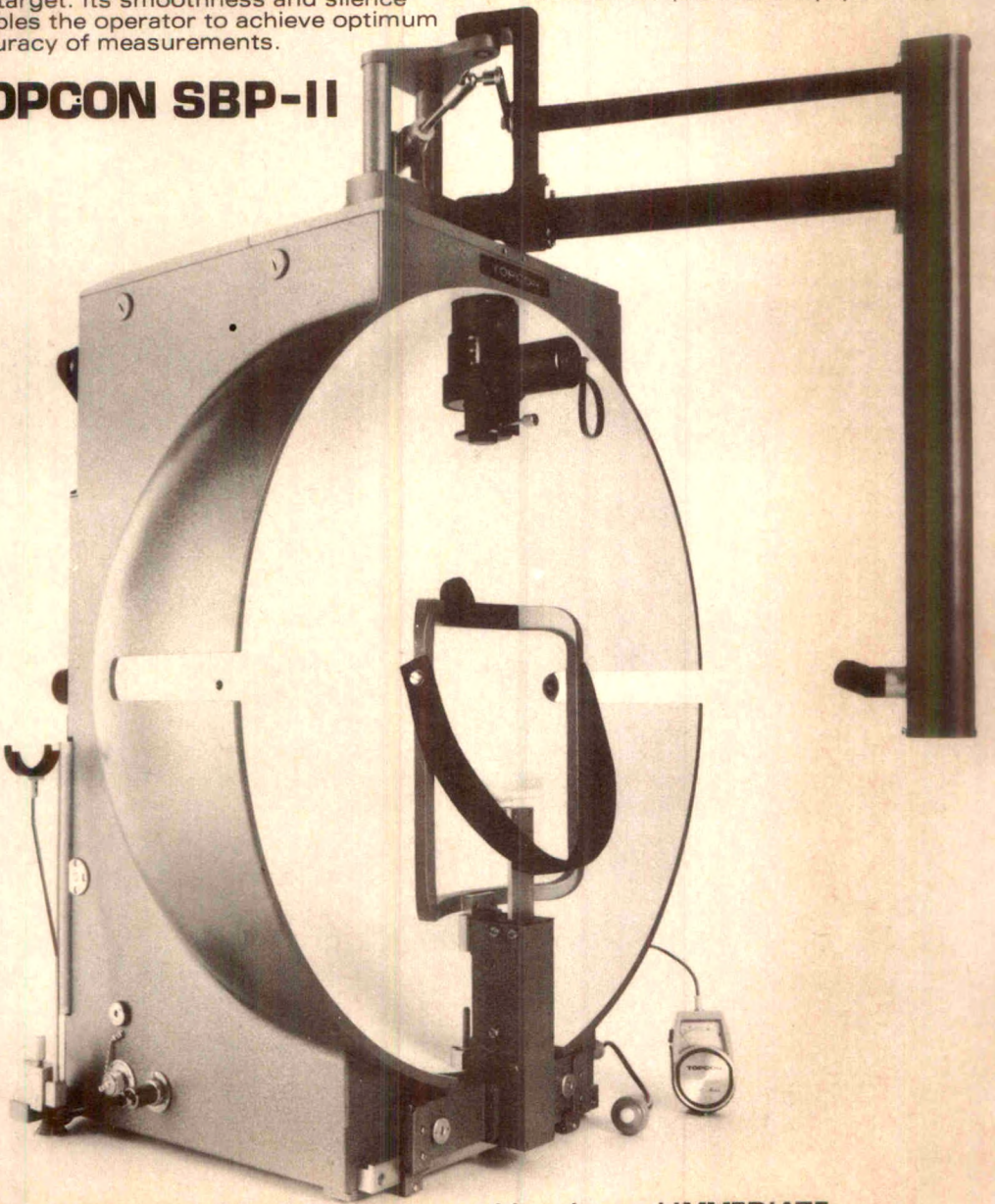
- The SBP-11 is recognized for its accuracy and ease of operation in critical perimetry field testing because of our constant monitoring for improvements made possible through new technological developments.

One such improved feature on the SBP-11 is a new device for occluding the target. Its smoothness and silence enables the operator to achieve optimum accuracy of measurements.

Other significant advantages of the SBP-11 include:

- Reproducible environmental conditions for accuracy in subsequent examinations.
- Constant monitoring of patient's fixation with sighting telescope.
- Automatic recording probe with manual override (standard equipment.)

TOPCON SBP-11



These features combined with a reasonable price and IMMEDIATE AVAILABILITY should make the Topcon SBP-11 your first choice for keeping in step with today's sophisticated diagnostic techniques. Contact your Topcon distributor or write us for details.

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Peter can't play any position.



Accommodative esotropia may prevent a child from developing the skills necessary for competitive sports. Lack of binocular single vision may affect school work as well as play...and negative cosmetic effects may alter peer relationships.

Phospholine Iodide (echothiophate iodide) may be able to change the lineup.

Diagnosis... To help determine if there is an accommodative basis for the esotropia, one drop of PHOSPHOLINE IODIDE 0.125% may be instilled daily in each eye, prior to retiring, for two or three weeks.

Treatment... If there is a significant accommodative factor present, the continued use of PHOSPHOLINE IODIDE alone is often sufficient for treatment, as long as the drug is well tolerated. PHOSPHOLINE IODIDE acts by altering the accommodative convergence/accommodation relationship in a favorable way, so that near vision is obtained with less accommodative effort, and fusion can be maintained.

If surgery is necessary, postoperative use of PHOSPHOLINE IODIDE may help correct a residual deviation.

Phospholine Iodide®

(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)

in the diagnosis and treatment of accommodative esotropia

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PHOSPHOLINE IODIDE®
(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: 1. Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.
Accommodative esotropia—Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.
2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.
3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or in the respiration of the neonate.
2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.
3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.
2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.
3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.
4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.
5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.
6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.
7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.
2. Retinal detachment has been reported occasionally.
3. Activation of latent iritis or uveitis may occur.
4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.
5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.
6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.
7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.

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New York, N.Y. 10017

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Intraocular Contact Lens

CONTACT LENS AND CONTACT DEVICE

THURSDAY, NOVEMBER 6TH AND
FRIDAY, NOVEMBER 7TH, 1975

From 8:00 to 12:00 noon each day symposia will be conducted by well known experts on advances in hard and soft contact lenses, therapeutic soft contact lenses, use of contact lenses as a surgical adjunct, hard and soft contact lens hygiene and new developments in contact lens materials.

INTRAOCULAR LENS SYMPOSIA AND COURSE

SATURDAY, NOVEMBER 8TH, 1975

The entire day from 8:00 to 5:30 P.M. will be devoted to in-depth study of intraocular lens surgery, technology and quality control.

The morning symposia on intraocular lens subjects will be conducted by nationally recognized experts in the field.

In the afternoon, well known instructors will present an intensive practical course in intraocular lens surgery and management.
Course instruction time: 4½ hours

COURSES

The following intensive, instructional courses will be offered. Each course will be taught by well known instructors in the field.

1. BASIC COURSE IN HARD AND SOFT CONTACT LENS FITTING

A practical review of all you need to know to get started fitting hard and/or soft contact lenses. The course will also cover the basics of aphakic hard and soft contact lens fitting.
Total instruction time: 9 hours

2. ADVANCED CONTACT LENS FITTING

Designed for those who are already initiated in hard and/or soft contact lenses but would like to gain more practical experience in such disciplines as: keratoconus fitting, correction of presbyopia (bifocals), photokeratoscopy, toric lenses.
Instruction time: 9 hours

3. THERAPEUTIC SOFT CONTACT LENSES

A practical presentation of the principles and practice of therapeutic soft contact lens fitting. The course also includes drug delivery by contact devices and continuous wearing of lenses.
Instruction time: 9 hours

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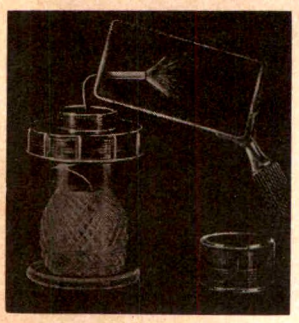
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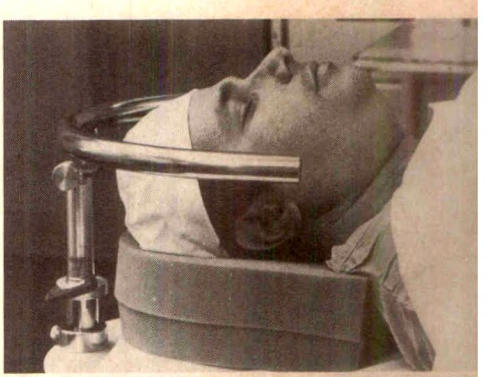
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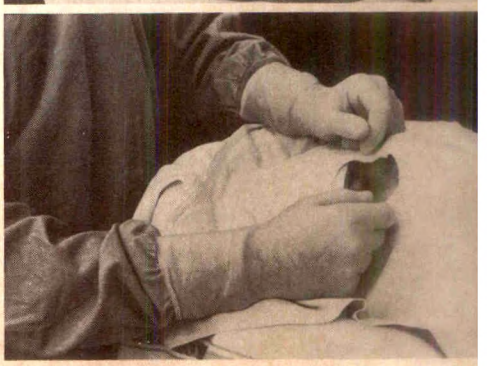
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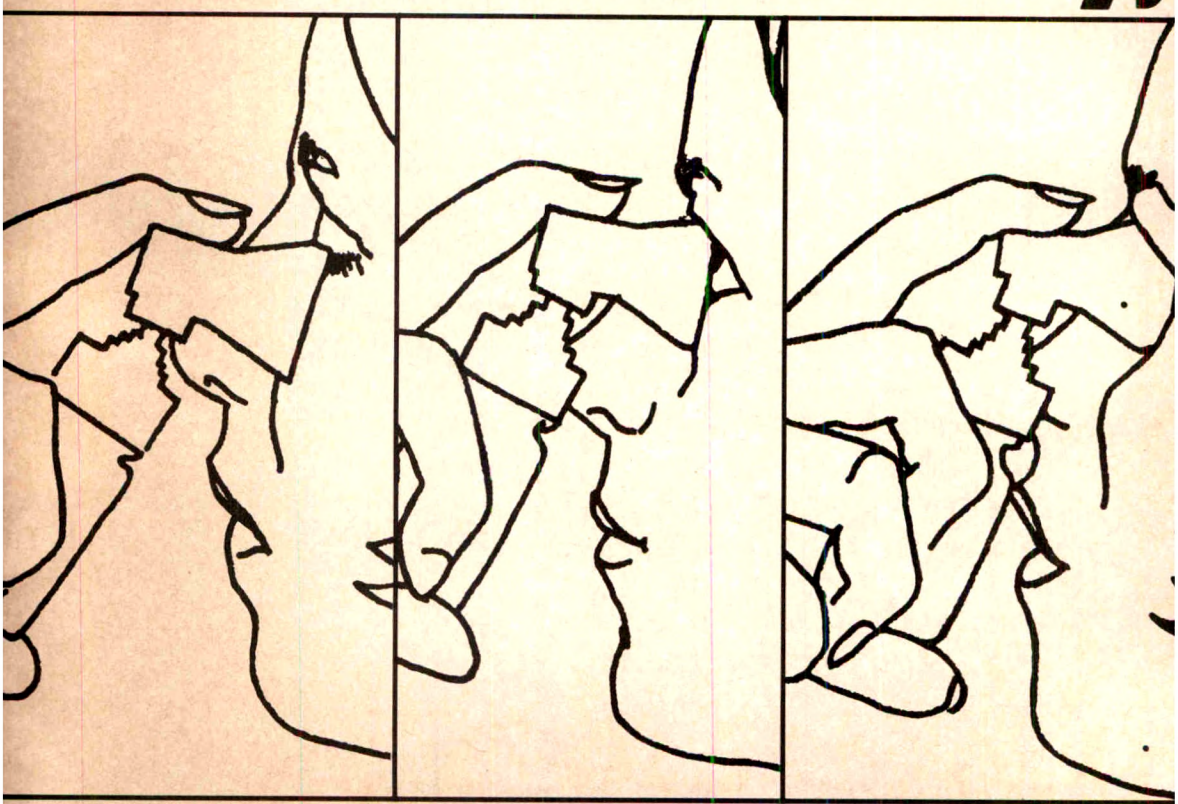
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Average applanation tonometry readings of 22 glaucoma patients treated first with pilocarpine drops—and then with pilocarpine mist (MISTURA® P Pilocarpine HCl).*

TONOMETRY READINGS (mm/Hg)					
On drops prior to treatment with mist		Approximately 1 month after start of treatment with mist		Two to four months after start of treatment with mist	
R. eye	L. eye	R. eye	L. eye	R. eye	L. eye
17.9	18.2	18.5	19.0	18.2	18.6
12-22	14-24	13-24	16-28	12-26	12-24

*Drug Delivery Systems for Topical Ophthalmic Medication, by G. Peter Halberg, M.D., FACS, Stephen E. Kelly, M.D., Michael Morrone, M.S., Annals of Ophthalmology, September, 1975.

Tonometrically,



Hold MISTURA between index finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

Gently retract the lid. Be sure that the bottom of the eyescope rests on the orbital bone. Look up within the eyescope.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.

46 patients with chronic simple open angle glaucoma who initially used pilocarpine drops and then changed to pilocarpine mist (MISTURA P Pilocarpine HCl).†

	MEAN TONOMETRY READINGS (mm/Hg) AFTER TREATMENT WITH 1% PILOCARPINE (N=16)		2% PILOCARPINE (N=30)	
Time of reading	R. eye	L. eye	R. eye	L. eye
Drops				
1st weekly visit	17	17	20	20
2nd weekly visit	16	16	20	19
Mist (MISTURA)				
3rd weekly visit	16	16	20	19
4th weekly visit	16	16	20	19

†Data on file at Lederle Laboratories.

it's a draw

A better way to take a drop?

In two recent studies,*† glaucoma patients were switched from pilocarpine drops to MISTURA® P Pilocarpine HCl. In both studies MISTURA P was shown to be therapeutically equivalent in the control of intraocular pressure.

But MISTURA offers several unique advantages.

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When you compare MISTURA to drops, consider convenience.



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Please see prescribing information on last page of this advertisement

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev.7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with: benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for the difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES
1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 as a preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P *pilocarpine HCl* is indicated for:
1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

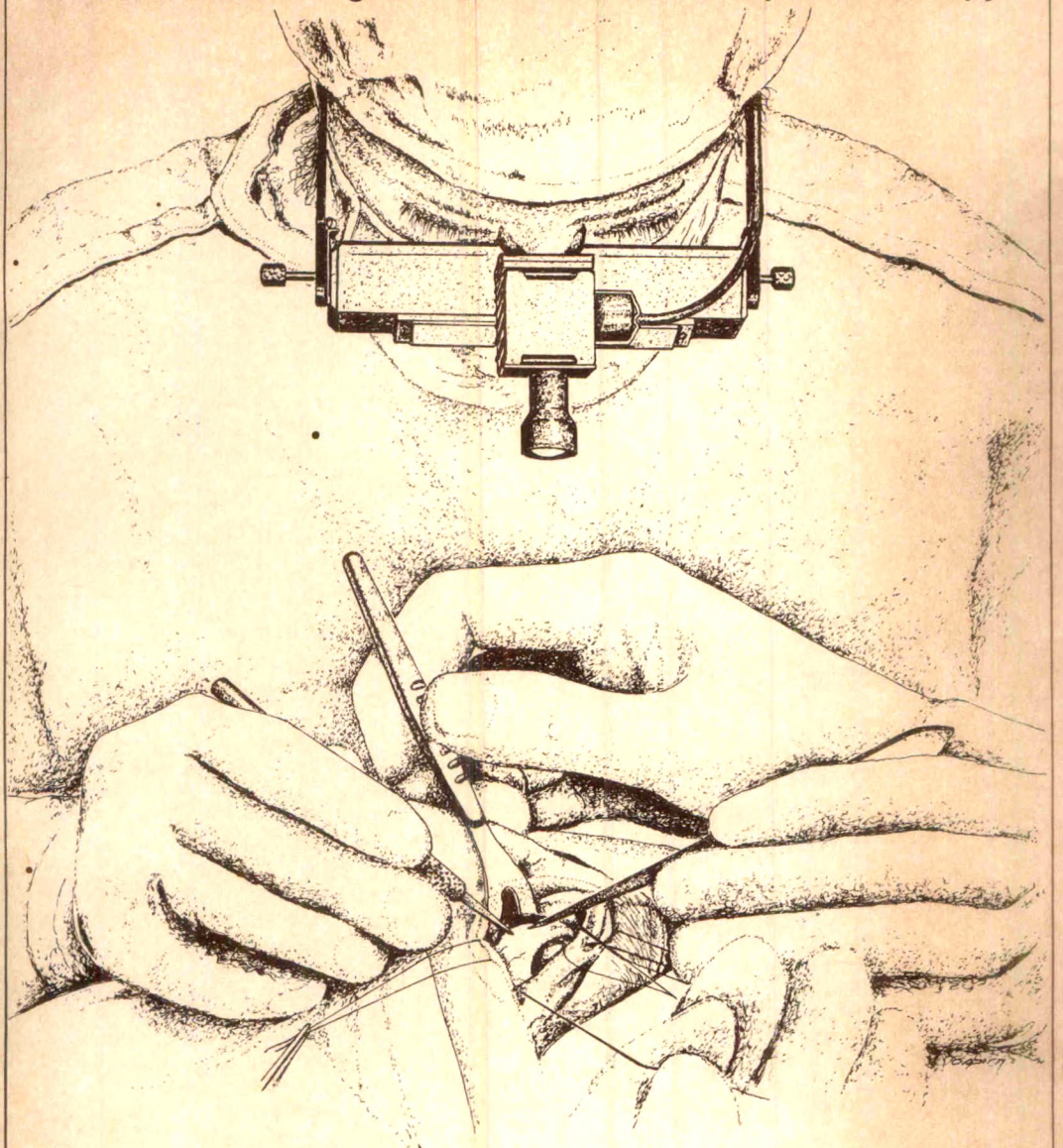
PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on prolonged use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:
1. For glaucoma, the recommended dosage is 1 mist application two to four times a day of the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations should be used.
3. The dosage and strength required to reverse mydriasis depends on the cycloplegic used.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

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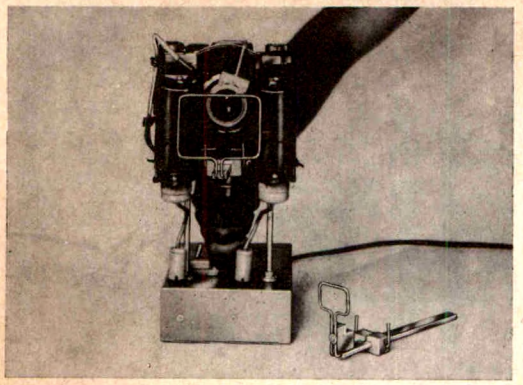
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(Epinephrine Base 0.55%)

E-PILO-4® Contains:
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in a buffered aqueous solution containing sodium bisulfite, mono- and dibasic sodium phosphate, and disodium edetate. **Indications:** For the treatment of glaucoma; more specifically, the chronic simple glaucoma of the open angle type. **Contraindications:** Contraindicated in narrow angle glaucoma. **Warning:** FOR TOPICAL OPHTHALMIC USE ONLY. If irritation develops, patients should be advised to discontinue use and consult prescribing physician. **Precautions:** Use with caution in unverified glaucoma and vascular hypertension. Epinephrine compounds are effective in the management of many of the forms of glaucoma; but complications, especially conjunctival irritation, occur frequently. If the reaction is severe, discontinuance of the drug may become necessary. This solution is sterile when packaged. To prevent contaminating dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of the bottle. Keep bottle tightly covered when not in use. Keep in cool place. Protect from light. Do not use if solution has darkened. **Dosage:** One or two drops on awakening and in the evening. If this fails to control the pressure, medication may be used more frequently. The frequency of instillation and the concentration depends on the response of the patient. The ophthalmologist must ascertain just how much **E-PILO** is necessary for each individual patient. **Caution:** Federal law prohibits dispensing without prescription. **How Supplied:** 10 ml. plastic squeeze bottle with dropper tip.

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Prescribing information on facing page.

NEURO-OPHTHALMOLOGY TAPES

by

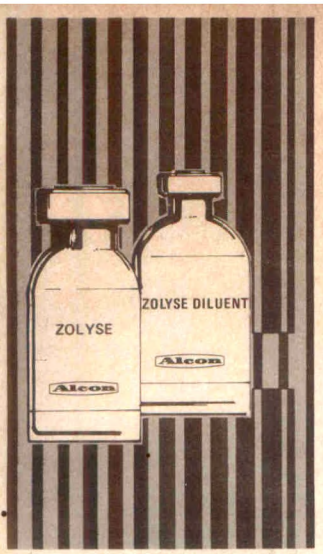
J. Lawton Smith, M.D.

1. The Neuro-ophthalmologic Exam
2. Third Nerve Disease
3. Visual Fields
4. Nystagmus
5. Thyroid Eye Disease
6. The Pupil
7. The Eye in Strokes
8. Late Ocular and Neurosyphilis
9. Optic Nerve Disease #1
10. Optokinetic Nystagmus
11. Skew Deviation
12. Pediatric Neuro-ophthalmology
13. Migraine
14. Convergence Insufficiency
15. Pseudotumor Cerebri
16. Functional Visual Loss
17. The Diplopia Work-Up
18. The Eye in Encephalocele
19. Hydrocephalus
20. Optic Nerve Disease #2
21. Neurosurgery
22. Visual Loss Work-Up
23. Congenital Nystagmus Therapy
24. Blepharospasm
25. Neuro-ophthalmologic History
26. The Eye in Nasopharyngeal Tumors
27. Refraction in Neuro-ophthalmology
28. References and Answers to Letters
29. Internuclear Ophthalmoplegia
30. Opticians Gems #1
31. More of #30 Plus More N-O Gems
32. Opticians Gems #2
33. Fourth Nerve Disease
34. Neuroradiology #1
35. Fifth Nerve Disease
36. Neuro-ophthalmology Update 1975
37. EMI Scan
38. Basic Ocular Motility for Neurologists #1
39. Basic Ocular Motility for Neurologists #2
40. The Orbit
41. Intraocular Lenses #1 (Dr. Jaffe)
42. Intraocular Lenses #2 (Dr. Jaffe)
43. Diabetic Retinopathy—Photocoagulation (Dr. George Blankenship)
44. Diabetic Retinopathy—Vitrectomy (Dr. George Blankenship)
45. Red Hot Practice Pearls (office assistant)
46. Adie's Pupil, Amsler Grid & Rubella Gems
47. Headaches
48. Optic Atrophy after Cataract Surgery
49. New "4-drop Aspheric" Cataract Lens #1 (Dr. Robert Welsh)
50. "4-drop Aspheric" Cataract Lens #2 (Dr. Welsh)
51. Sixth Nerve Disease
52. Downbeat Nystagmus and Hereditary Ataxias
53. Exposure Keratitis
54. Horner's Syndrome
55. Chiasm Mystery Case

These tapes are aimed strictly at the clinician. They will help with your continuing medical education, for they have been approved for AMA Physicians Recognition Award in category 5(a) on a hour-for-hour basis up to the 22 hour limit in this subcategory. Most important of all, they save you TIME. You can listen to the cassettes in the car en route to hospital, etc., and save that valuable study time in the evenings to spend with your family. They are timely—often with material over a year ahead of journals. Not all tapes are aimed at the same audience. Tapes 38-39 are for neurologists and neurosurgeons and would be boring to ophthalmologists. Tapes 14, 30, 31, 41, 42, 43 & 44 are aimed at ophthalmologists and would be boring to neurologists and neurosurgeons. The cost of the tapes is $8 each, postage paid (U.S. and Canada). All other countries add $10 for airmail for the total order. All orders must be prepaid in U.S. currency. These tapes are not to be reduplicated or sold. To order, circle the tapes above you want, make check out to Neuro-ophthalmology Tapes and mail to **Neuro-ophthalmology Tapes, 9820 S.W. 62 Court, Miami, Florida 33156, U.S.A.**

We have a new little pocket sized book entitled **The Pupil.** Send $3.95 to J. L. Smith, M.D., 9820 S.W. 62 Court, Miami, Florida 33156, and this will be sent to you promptly. For an optokinetic tape, send $5 to "Fletchers Optokinetic Flags," 6250 S.W. 98 Street, Miami, Fla. 33156. Residents of Florida please add 4% sales tax. For a small, reasonable quality projector light pointer, send $9.95 to Dr. J. A. McCrary, Texas Children's Hospital, P.O. Box 20269, Houston, Texas 77025.

A TWO-DAY COURSE "OFFICE NEURO-OPHTHALMOLOGY" will be in HOUSTON NOVEMBER 6-7, 1975. For details write to Dr. J. A. McCrary, P.O. Box 20269, Houston, Texas 77025.





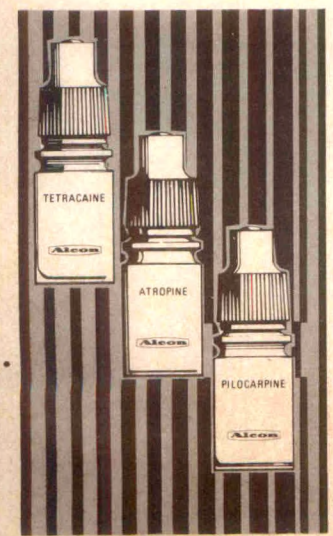




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CATARACT WORKSHOP

Phakoemulsification, Lens Implant, Vitrectomy and other modalities will be key subjects of a special workshop on **Cataract Surgery** at the 1976 AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY annual meeting (Feb. 29-Mar. 5, Americana Hotel, Bal Harbour/Miami Beach, Florida). The workshop will be presented in five afternoon sessions by Drs. Charles Kelman, Jack Hartstein, Norman Jaffe, Stanley Becker, Harvey Lincoff, Antonio Gasset and others.

The meeting will feature other workshops in Microsurgery and Stereoscopic Studies of the Anterior Segment; Contact Lenses in Aphakia and Corneal Diseases; Gonioscopy; Glaucoma; and Refraction.

More than 50 leading ophthalmologists will participate with the following chairmen: Cataract, David Paton; Retinal Diseases, Harvey Lincoff; Glaucoma, H. Saul Sugar; Cornea/External Diseases, Claes Dohlman; Pediatric Ophthalmology, Donelson Manley; Corneal Surgery, Herbert Kaufman; and Oculoplastic Surgery, Pierre Guibor. Jules Francois is Chairman of the entire meeting. Registrants earn 40 or more credit hours in CME.

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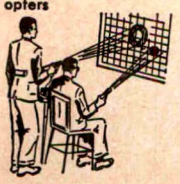
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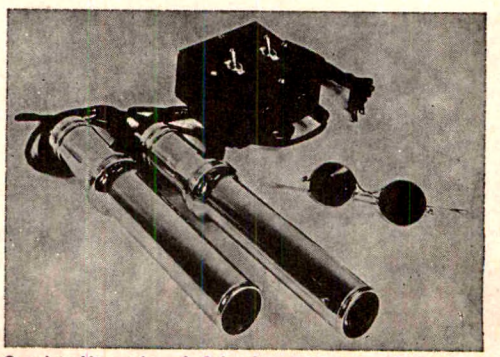
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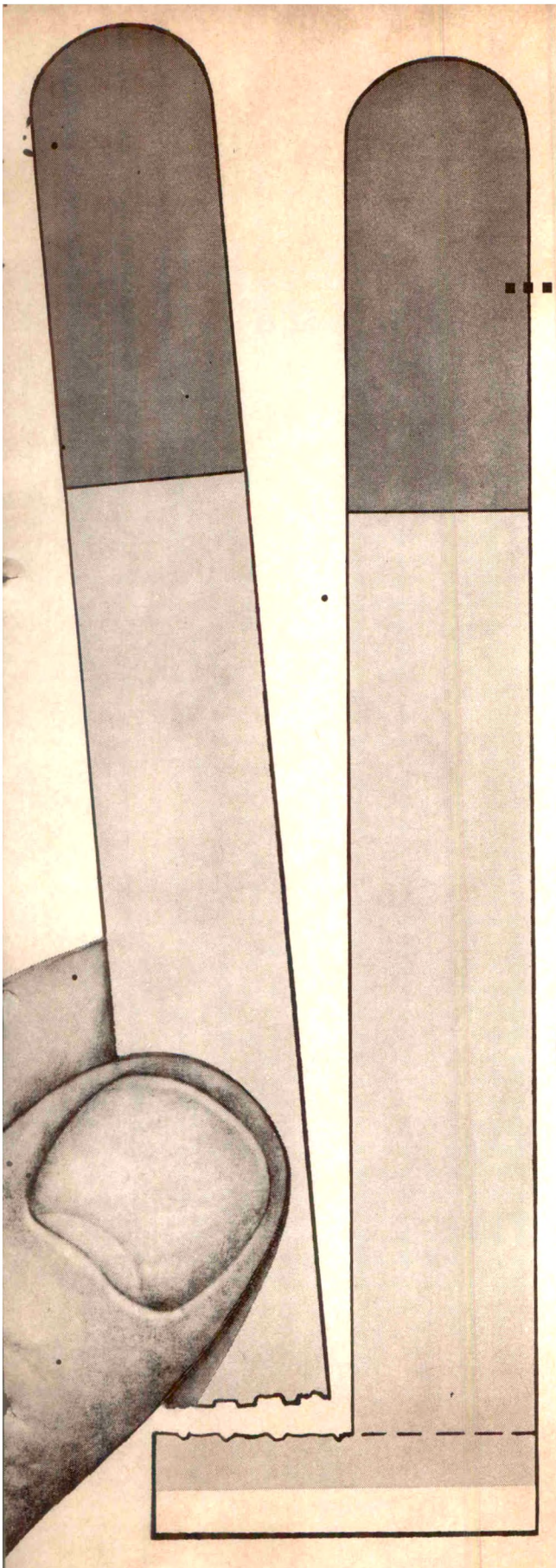
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at

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Course Includes: Animal Surgery, Complications, Patient Selection, Post Operative Patient Examination, Round Table Discussion, Ten Live Cases, Variation in Technique.

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Edwin Hill, M.D.
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James Little, M.D.

Guest Faculty

Mr. Eric Arnott
Ronald Barnet, M.D.
Gilbert W. Cleasby, M.D.
William S. Harris, M.D.
Francis G. Hurite, M.D.
William M. McReynolds, M.D.
Donald Praeger, M.D.
John Sheets, M.D.

Course Dates: October 2-4, 1975, November 13-15, 1975, December 11-13, 1975.

Please Detach and Mail to

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2222 Santa Monica Blvd.
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Please send me further information. I am interested in the course for
October ☐, November ☐, December ☐.
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Introduced in the *American Journal of Ophthalmology (Vol. 53, page 520, 1962)*, this is the original Pigtail Probe used for reconstruction of torn tear ducts Featuring either a hook or hole configuration.

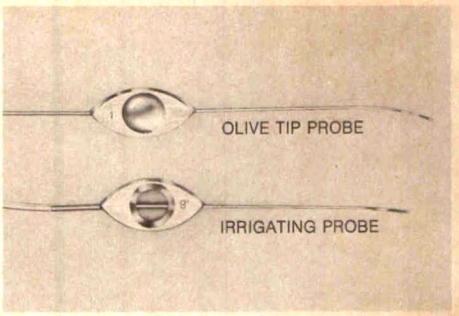
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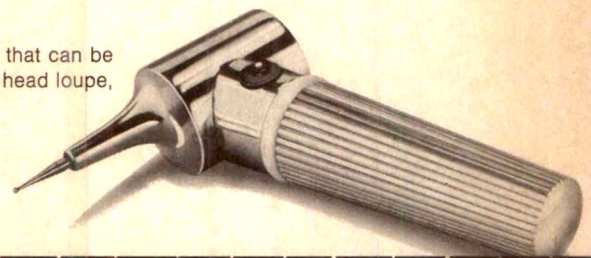


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Advanced Course

Presented by

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Under the auspices of

The Southern California Lions Eye Institute

at

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Santa Monica California

Course Prerequisite: Completion of a basic course in phacoemulsification.
Enrollment limited to six participants per course.
Credits: One Hour CMA Category A Fee $750.00
Featuring: A presentation of 10 live cases. Arrangements can be made to furnish you with a specially designed video camera for use in tape recording the cases you wish to have critiqued.
Course Director: Robert M. Sinskey, M.D.
Instructors: Richard Kratz, M.D. Robert M. Sinskey, M.D.
Course Dates: December 4-5, 1975, February 12-13, 1976
April 15-16, 1976, June 17-18, 1976

Please Detach and Mail to

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Please enter my reservation for the Advanced Phacoemulsification Course to be held during the month of

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My check for $750.00 is enclosed. ☐

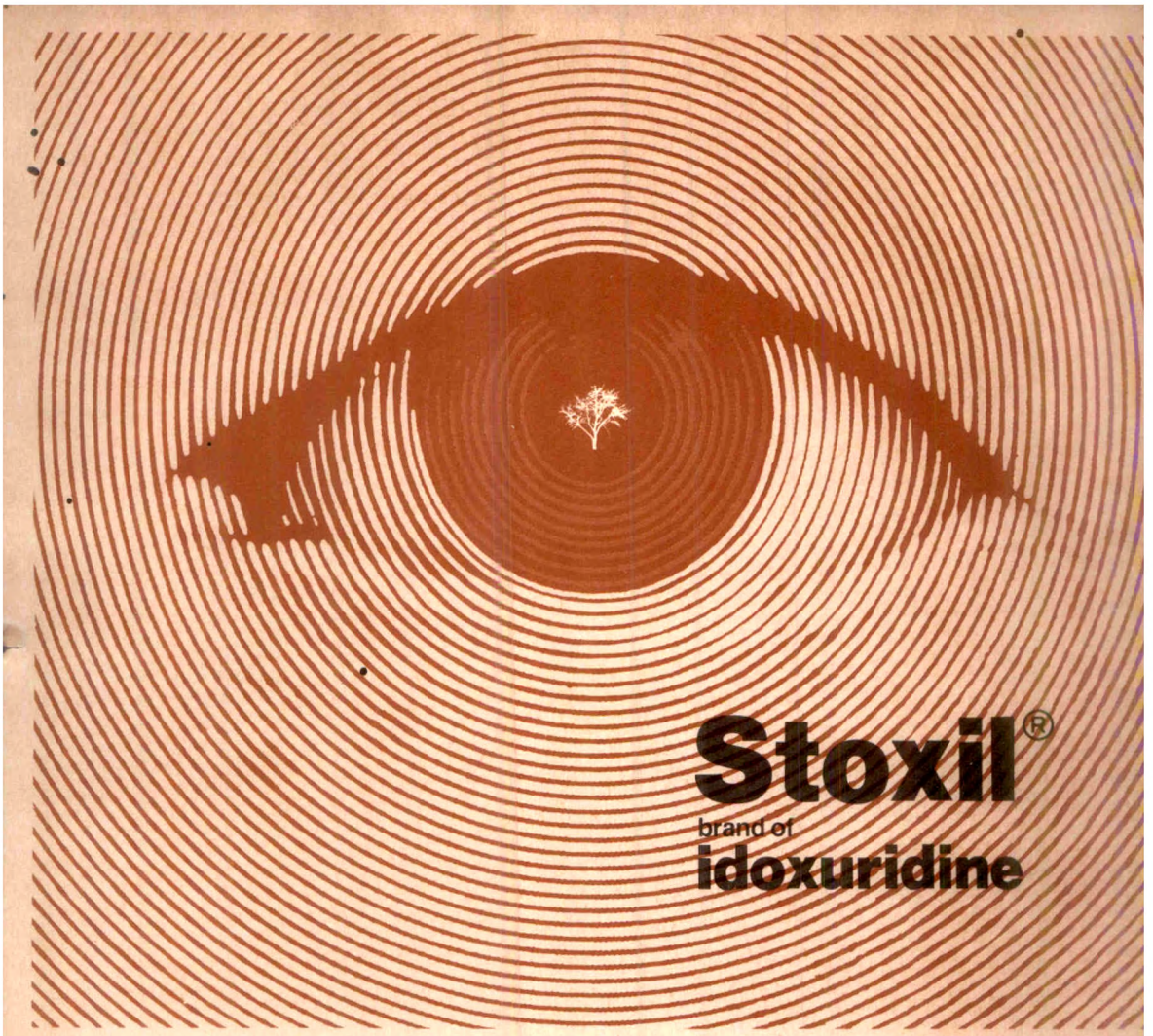
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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Only in the treatment of herpes simplex keratitis.

Description: 'Stoxil' Ophthalmic Solution contains idoxuridine (5-iodo-2'-deoxyuridine) 0.1% (1 mg./ml.) in distilled water; sterile when packaged. Preserved with thimerosal, 1:50,000. 'Stoxil' Ophthalmic Ointment contains idoxuridine 0.5% (5 mg./gram) in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

Contraindications: Contraindicated in patients with known or suspected hypersensitivity to any of its components.

Warning: Usage in Pregnancy—Idoxuridine should be administered with caution in pregnancy or in women of childbearing potential. Although teratogenic effects were reported in one study with rabbits when idoxuridine was instilled into the eye, these effects were not observed in a subsequent, more detailed study, even at doses substantially higher than those in the preceding study.

Precautions: Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

'Stoxil' Ophthalmic Solution should not be mixed with other medications.

Adverse Reactions: Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally, corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

How Supplied: 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

Stability: The Solution should be stored in refrigerator until dispensed. 'Stoxil' Ophthalmic Ointment does not require refrigeration.

Day and Night Stoxil® works against Herpes Simplex Keratitis

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Solution
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First, you can expect a high quality finished product. Each lens is lathe-cut from a button of highly stable three-dimensional polymer.

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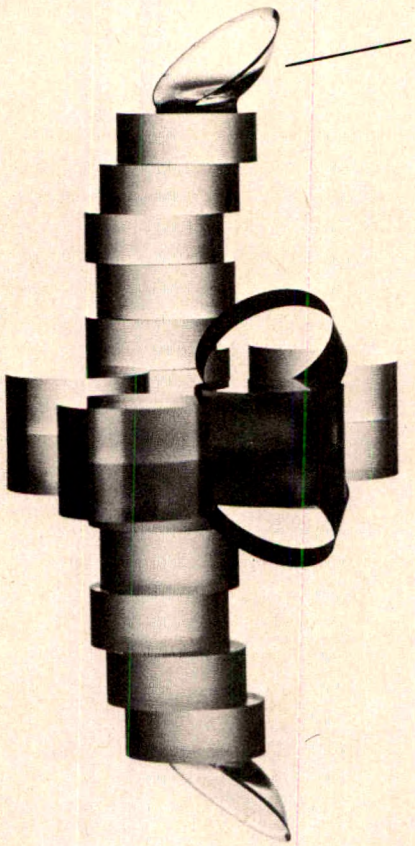
Yet this selection offers you a wide range of base curves and diameters. Enough to satisfy the majority of fitting problems in the correction of ametropia.

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To get complete information about Hydro-Curve™ products and supplies, call now, toll free (800) 854-2790 – in California (800) 542-6000. We're expecting your call.



The lathe-cut, soft, hydrophilic contact lens, now available from Soft Lenses, Inc.

The versatile one

HYDROCURVE™

(hefilcon A)

Contact Lens PHP*

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HydroCurve™ Soft Lenses, Inc. *PHP (U.S. Pat. 3,721,657) Trade Mark of Automated Optics, Inc.

HYDROCURVE™ (hefilcon A) CONTACT LENS

fabricated from PHP* polymer (poly (2-hydroxyethyl methacrylate) 46% Water 54%)

DESCRIPTION—The HydroCurve℠ (hefilcon A) Contact Lens PHP* is a hemispherical shell of approximately 14 mm. chord diameter and 0.1 to 1.0 mm. thickness. It consists of 46% poly (2-hydroxyethyl methacrylate) and 54% water by weight when immersed in normal saline.

ACTIONS—In its hydrated state a HydroCurve℠ (hefilcon A) Contact Lens PHP* becomes soft and pliable. When placed on the human cornea the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43.

INDICATIONS—HydroCurve℠ (hefilcon A) Contact Lenses PHP* are indicated for the correction of visual acuity in persons with nondiseased eyes who have spherical ametropias; refractive astigmatism of 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS—HydroCurve℠ (hefilcon A) Contact Lenses PHP* are contraindicated by the presence of any of the following conditions:

1. Acute and subacute inflammations of the anterior segment of the eye.
2. Any eye disease which affects the cornea or conjunctiva.
3. Insufficiency of lacrimal secretion.
4. Corneal hypoesthesia.
5. Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Medicants and Eye Drops: The HydroCurve℠ (hefilcon A) Contact Lens PHP* must be stored ONLY in BOILnSOAK℠ Solution. No ophthalmic solutions or medicants, including conventional contact lens solutions, can be used by HydroCurve℠ (hefilcon A) Contact Lens PHP* wearers prior to or while the lens is in place on the eye. Also, no solutions, including conventional contact lens solutions, other than BOILnSOAK℠ and the recommended cleaners BOILnSOAK℠ or Pliagel℠ or Soft/Mate℠ may be used on the HydroCurve℠ (hefilcon A) Contact Lens PHP* when the lens is off the eye.

Abrasions and Infections: If the lenses become less comfortable to the wearer than when they were first placed on the wearer's corneas, this may indicate the presence of a foreign body. The lens should be removed immediately and the patient examined. If any eye abrasion, ulceration, irritation or infection is present, a physician should be consulted immediately.

Lens Sanitation: Patients must adhere to recommended daily sanitary care of the HydroCurve℠ (hefilcon A) Contact Lenses PHP*. Failure to follow this procedure may result in development of serious ocular infections.

Wearing Restrictions: The HydroCurve℠ (hefilcon A) Contact Lens PHP* should be removed before sleeping or swimming or in the presence of noxious and irritating vapors.

Visual Blurring: When visual blurring occurs the lens must be removed until the condition subsides.

PRECAUTIONS

Storage: HydroCurve℠ (hefilcon A) Contact Lenses PHP* must be stored ONLY in BOILnSOAK℠ Solution. If left exposed to air, the lenses will dehydrate. If a lens dehydrates, it should be soaked in BOILnSOAK℠ Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: HydroCurve℠ (hefilcon A) Contact Lenses PHP* must be BOTH cleaned and disinfected daily. One procedure does not replace the other. CLEANING is necessary to remove mucus and film from the lens surface. This can be accomplished by using either BOILnSOAK℠ or Pliagel℠ or Soft/Mate℠ on a daily basis. Excessive deposits may damage the lens; therefore, if this occurs, review care of lens with patient.

DISINFECTING with the Hydrotherm℠ Patient Unit and BOILnSOAK℠ Solution has been shown to prevent the growth of certain organisms, namely Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Herpes simplex, on the lens and in the HydroCurve℠ Carrying Case with the porta-FLOW® Transfer Unit (basket).

HydroCurve℠ (hefilcon A) Contact Lenses PHP* must be cleaned daily with fresh BOILnSOAK℠ or Pliagel℠ or Soft/Mate.℠ Fresh BOILnSOAK℠ Solution must be used daily for storing the lenses. The HydroCurve℠ Carrying Case must be emptied and refilled with fresh BOILnSOAK℠ Solution just before disinfecting the lenses.

If a Hydrotherm℠ Patient Unit is not available for disinfecting the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.

Hygiene: Patients must be instructed to wash and rinse hands thoroughly, and dry with a lint-free towel before handling the lenses.

Cosmetics, lotions, soaps and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS—Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, patients may be instructed to apply a few drops of BOILnSOAK℠ Solution and wait until the lens moves freely before removing it.

Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms.

Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION—Conventional methods of fitting contact lenses do not apply to HydroCurve℠ (hefilcon A) Contact Lenses PHP*. For a detailed description of the fitting technique, refer to the HydroCurve℠ Fitting Guide, additional copies of which are available from: Soft Lenses, Inc., 8006 Engineer Road, San Diego, California 92111.

There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

Day	Maximum Wearing Time (Continuous Hours)	Day	Maximum Wearing Time (Continuous Hours)
1	3	8	8
2	3	9	8
3	4	10	10
4	4	11	12
5	6	12	14
6	6	13	15
7	8	14	all waking hours*

*Lenses should never be worn 24 hours a day.

Care must be taken on the initial visit to assure that the patient is supplied with a HydroCurve℠ Patient Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.



In Use Durability: With normal use and patient care, HydroCurve℠ (hefilcon A) Contact Lenses PHP* have been shown to be durable for a minimum of one year.

HOW SUPPLIED—Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the base curve, dioptric power, diameter, thickness and the manufacturing lot number of the lens.

To assure proper lens care and handling, each HydroCurve℠ patient must be supplied with a complete HydroCurve℠ Patient Care Kit.

The HydroCurve℠ Patient Care Kit is a package required for lens cleaning, disinfecting and storing consisting of the following:

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Patient Instructions	Cat. # 1007

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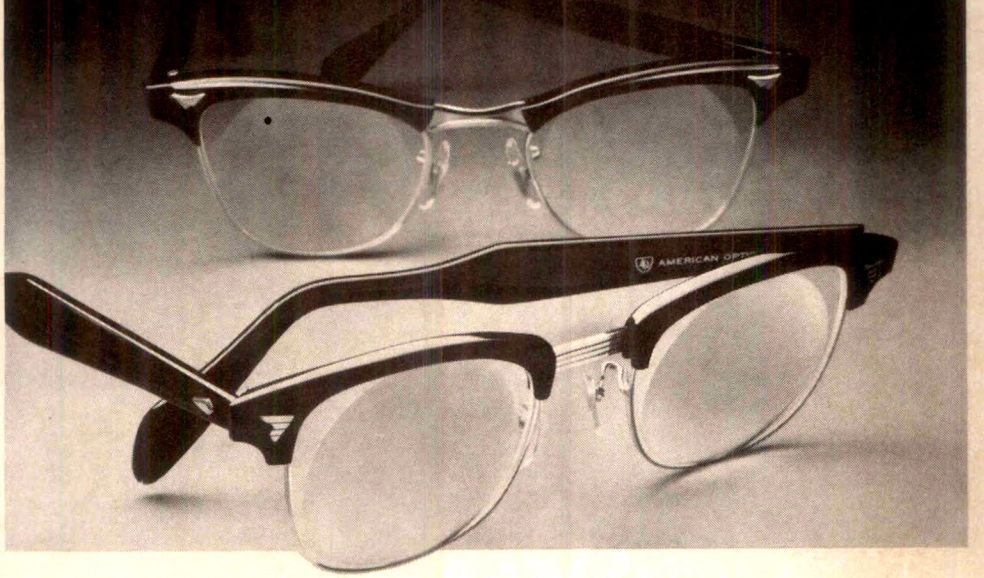
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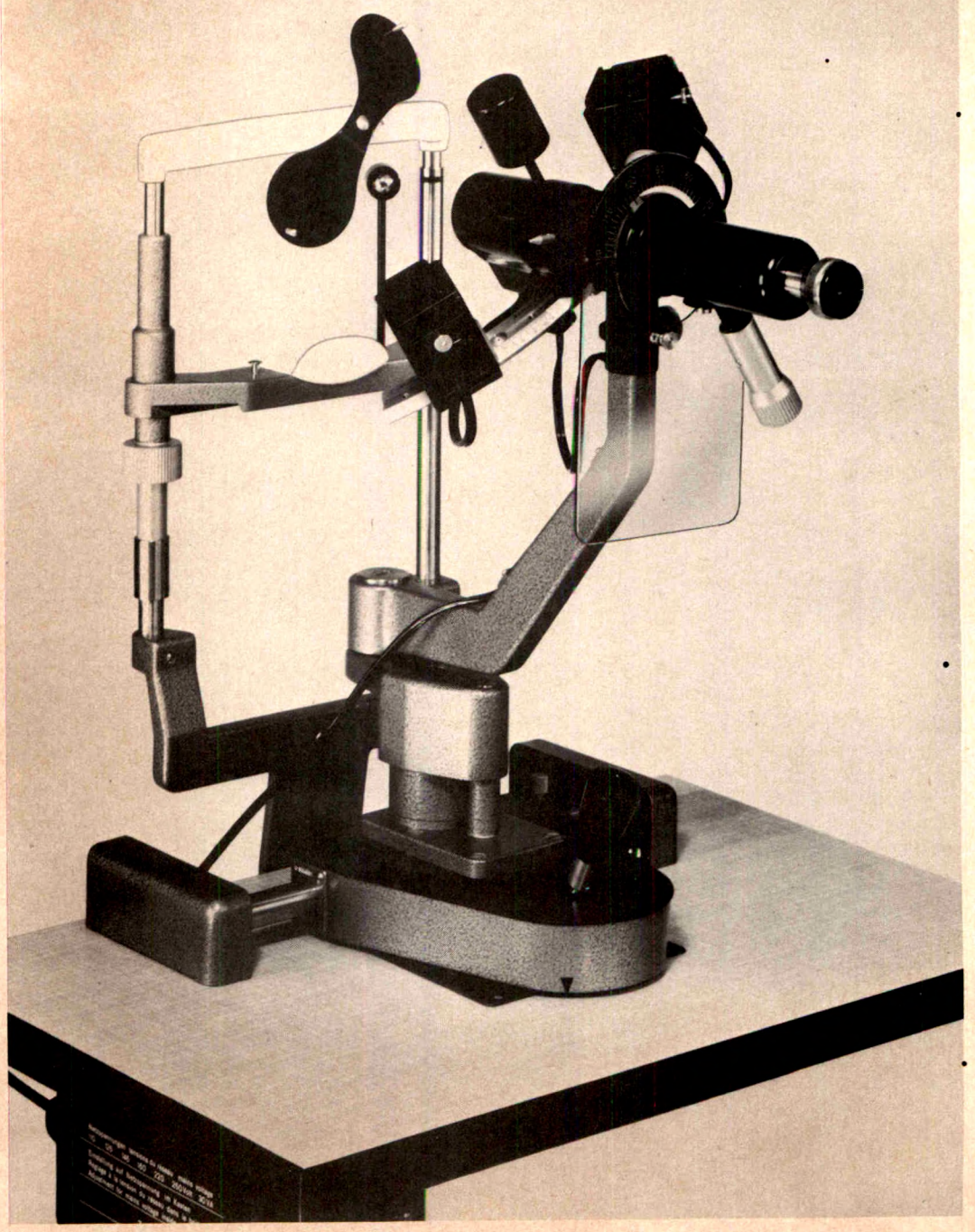
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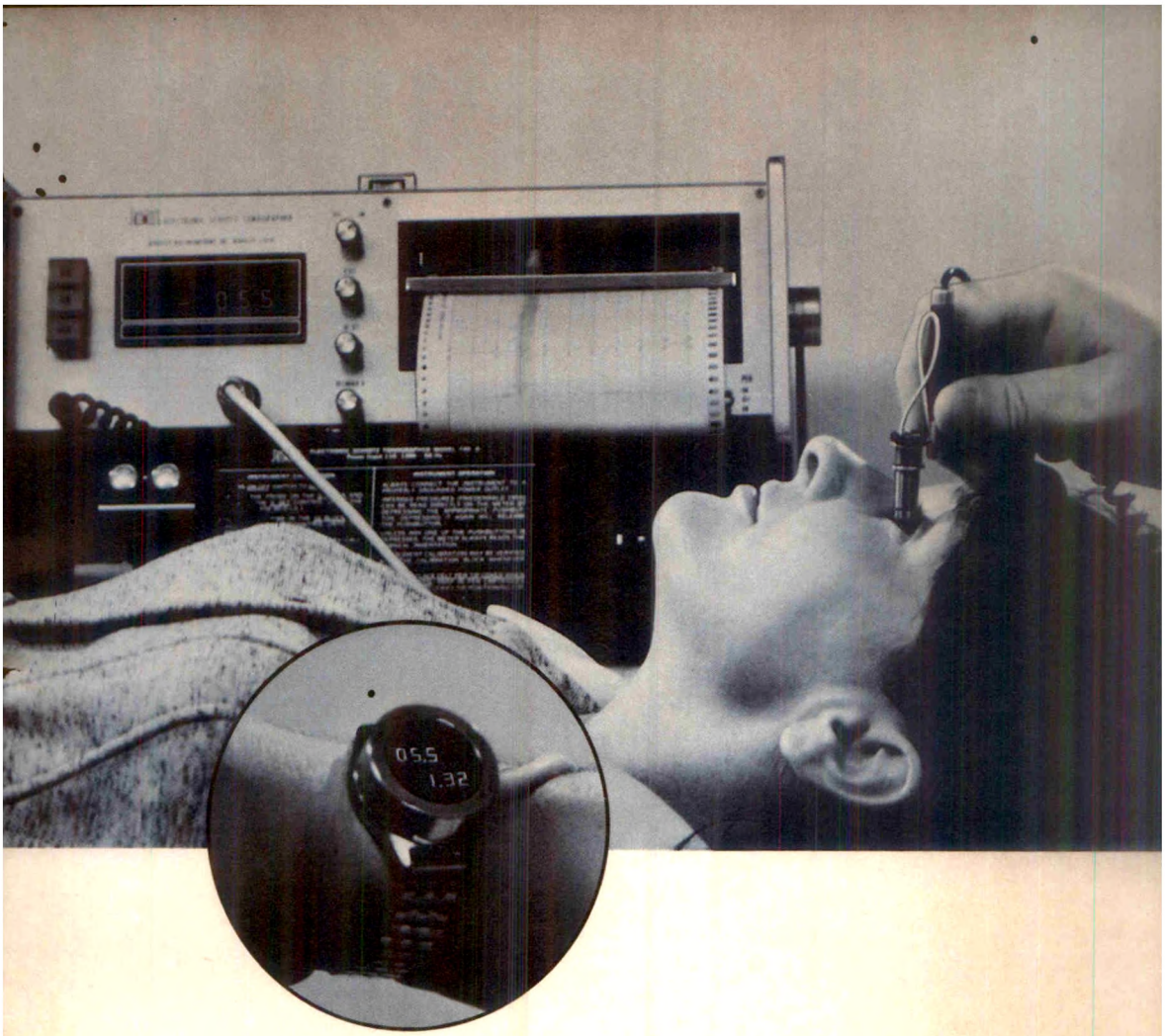
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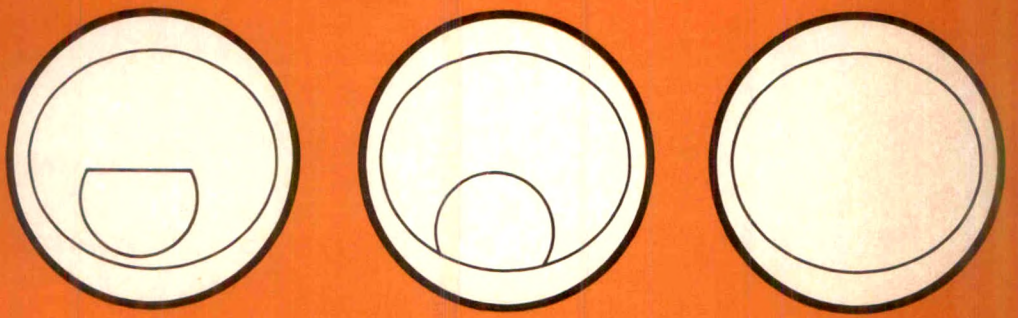
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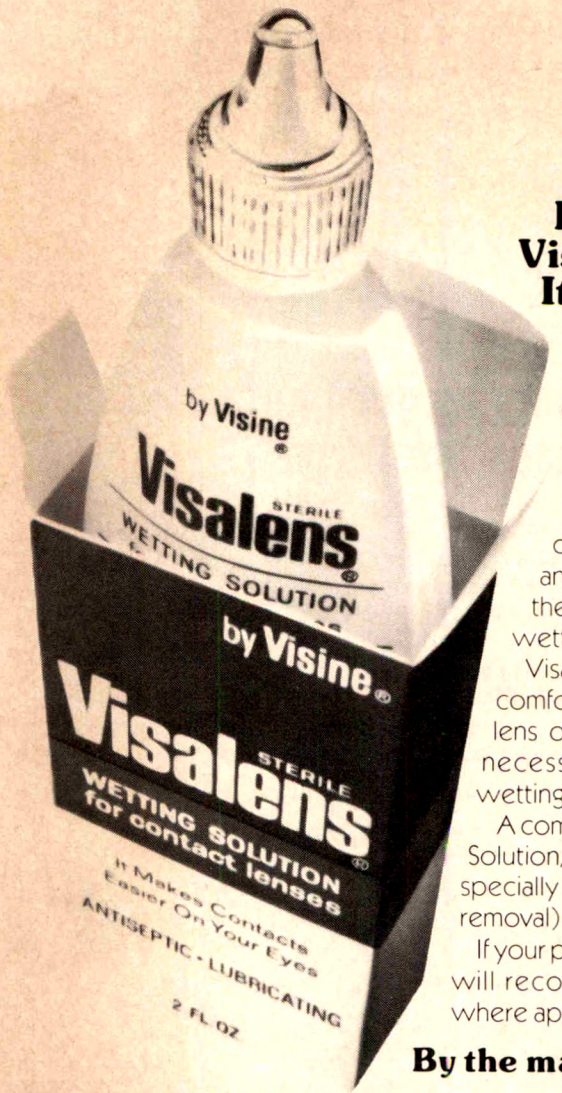


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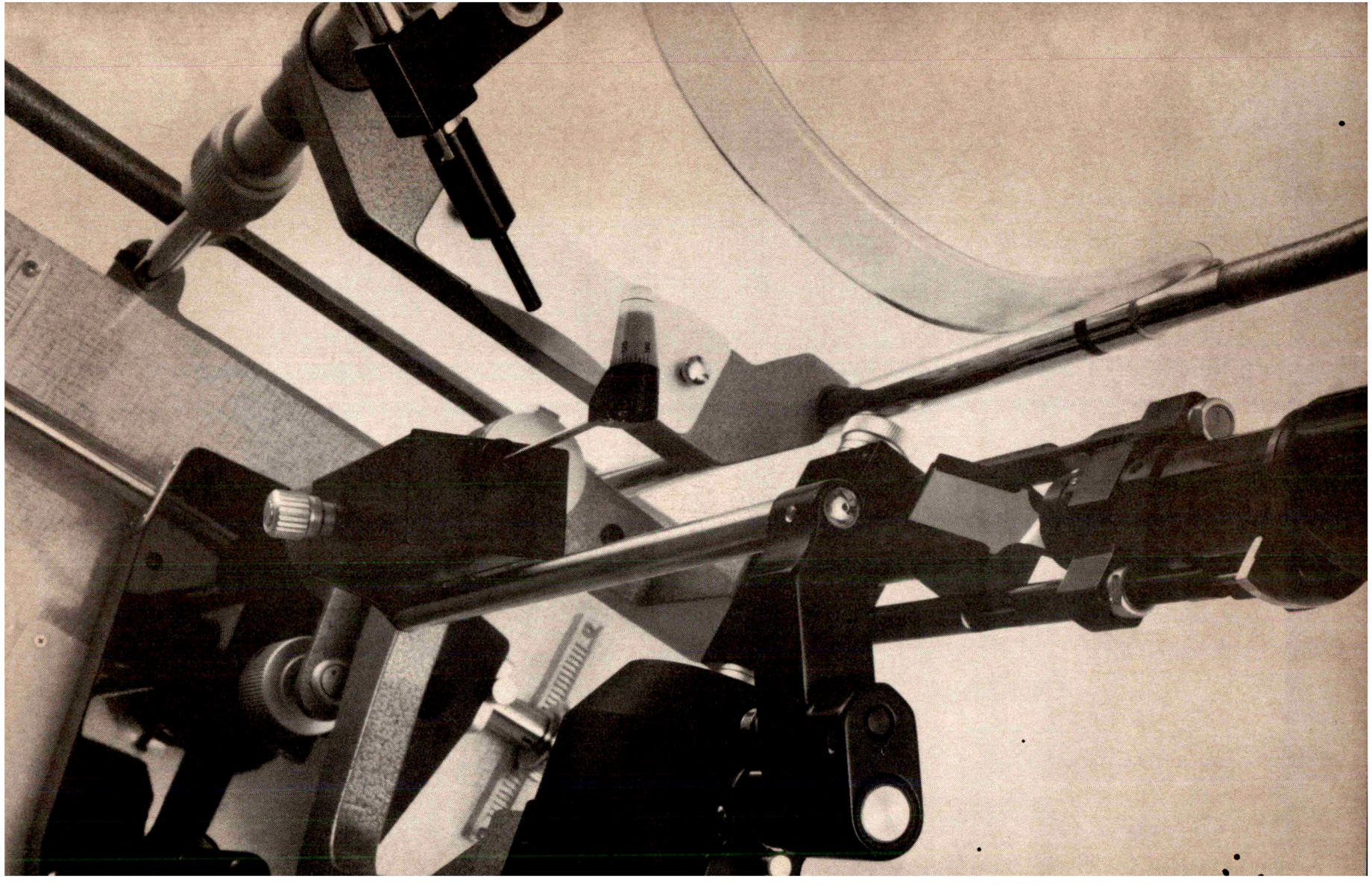
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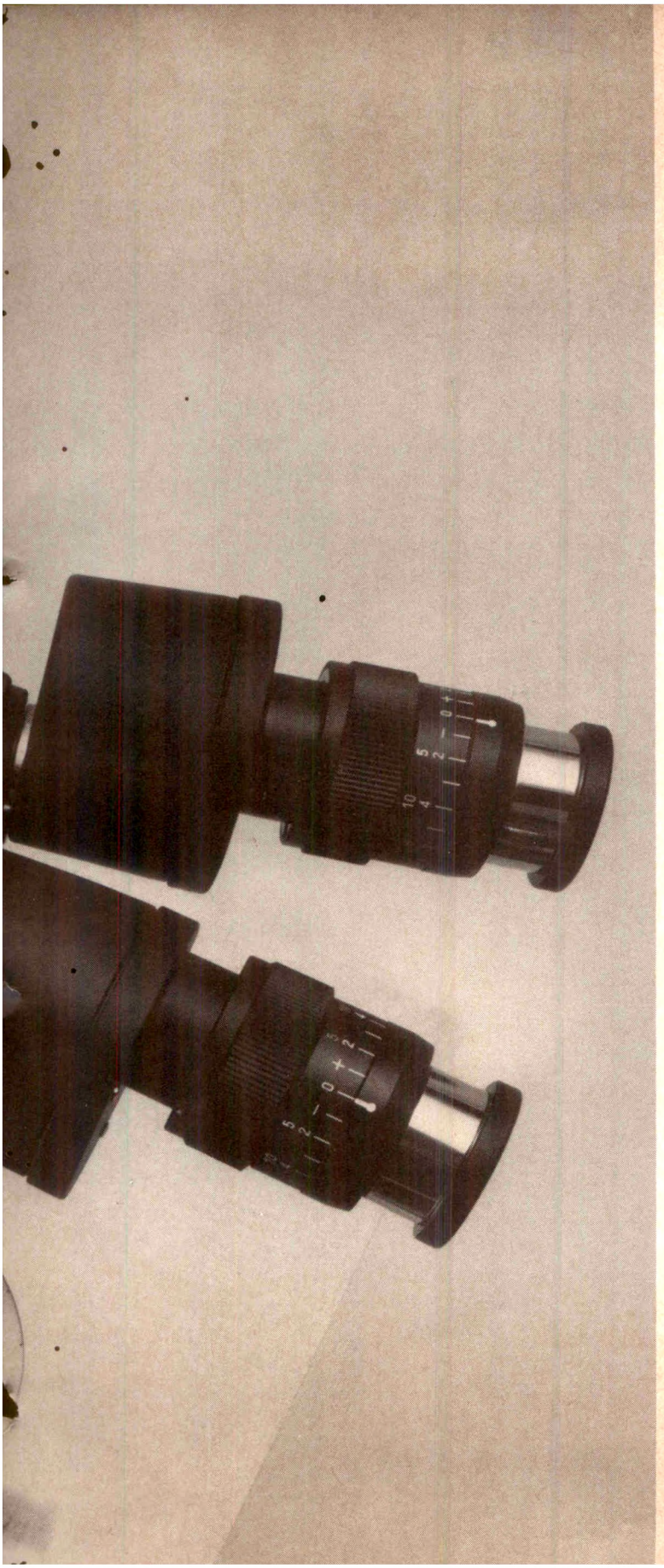
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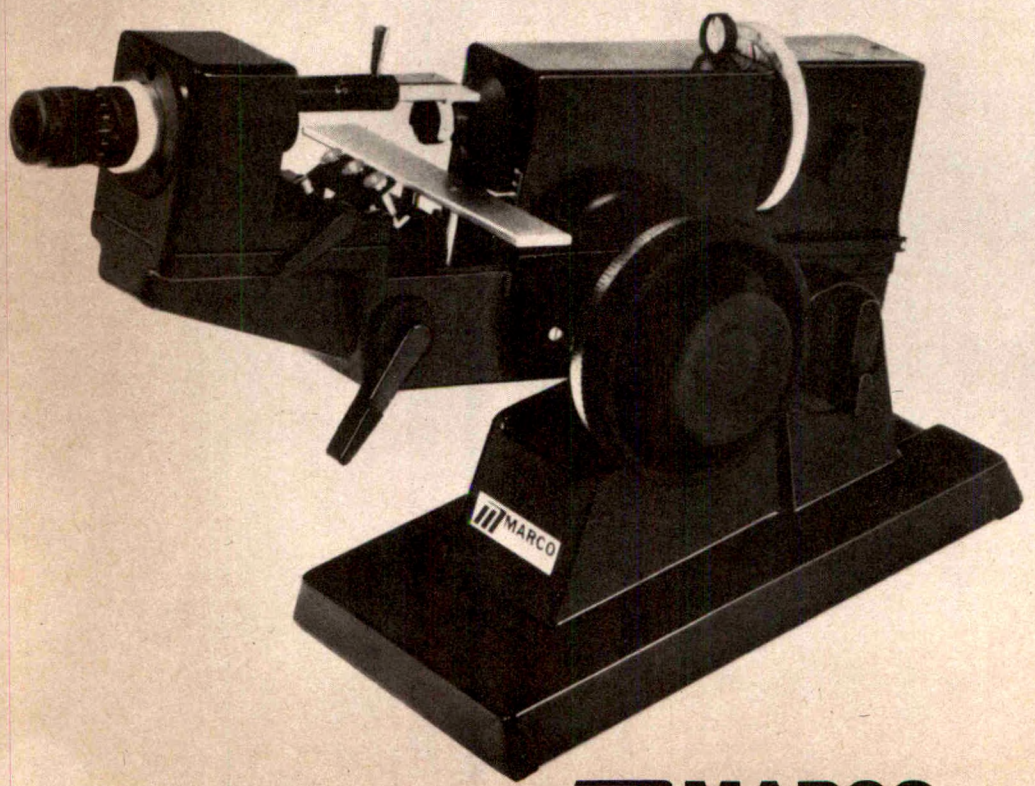
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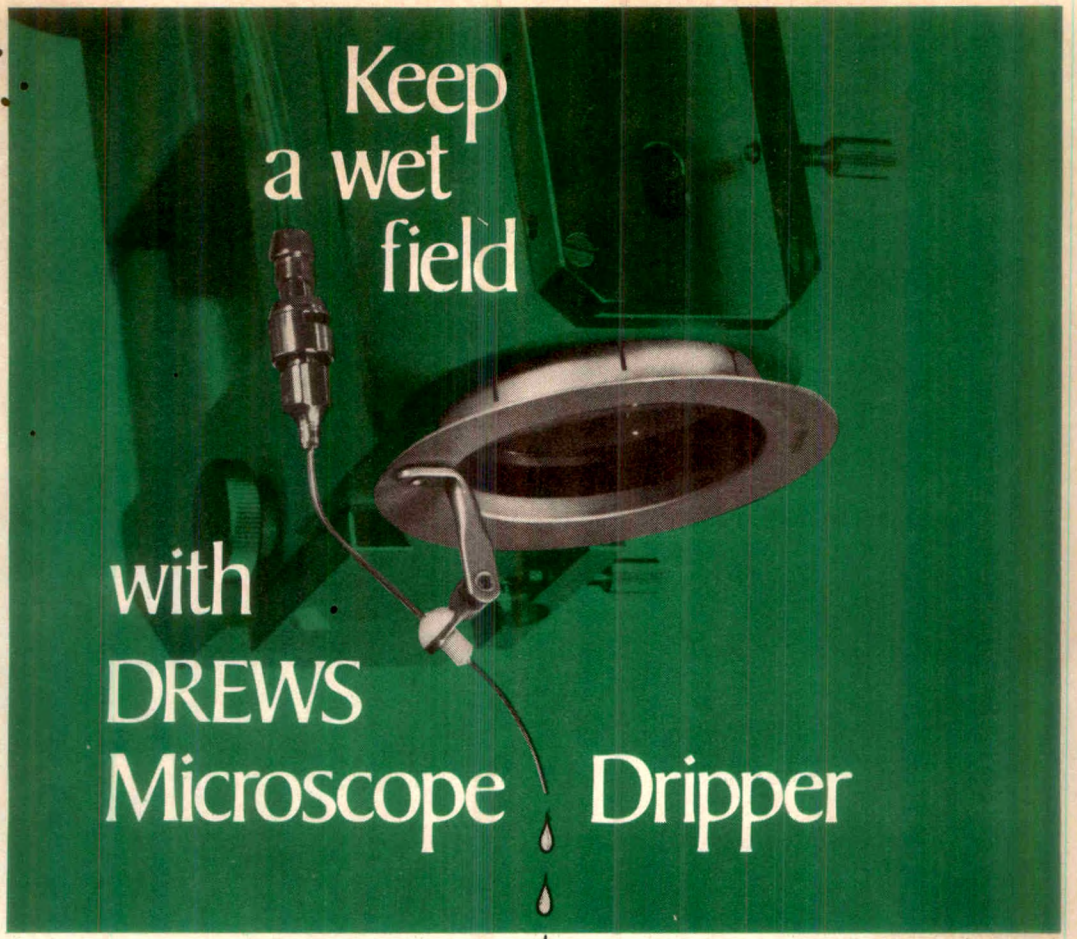
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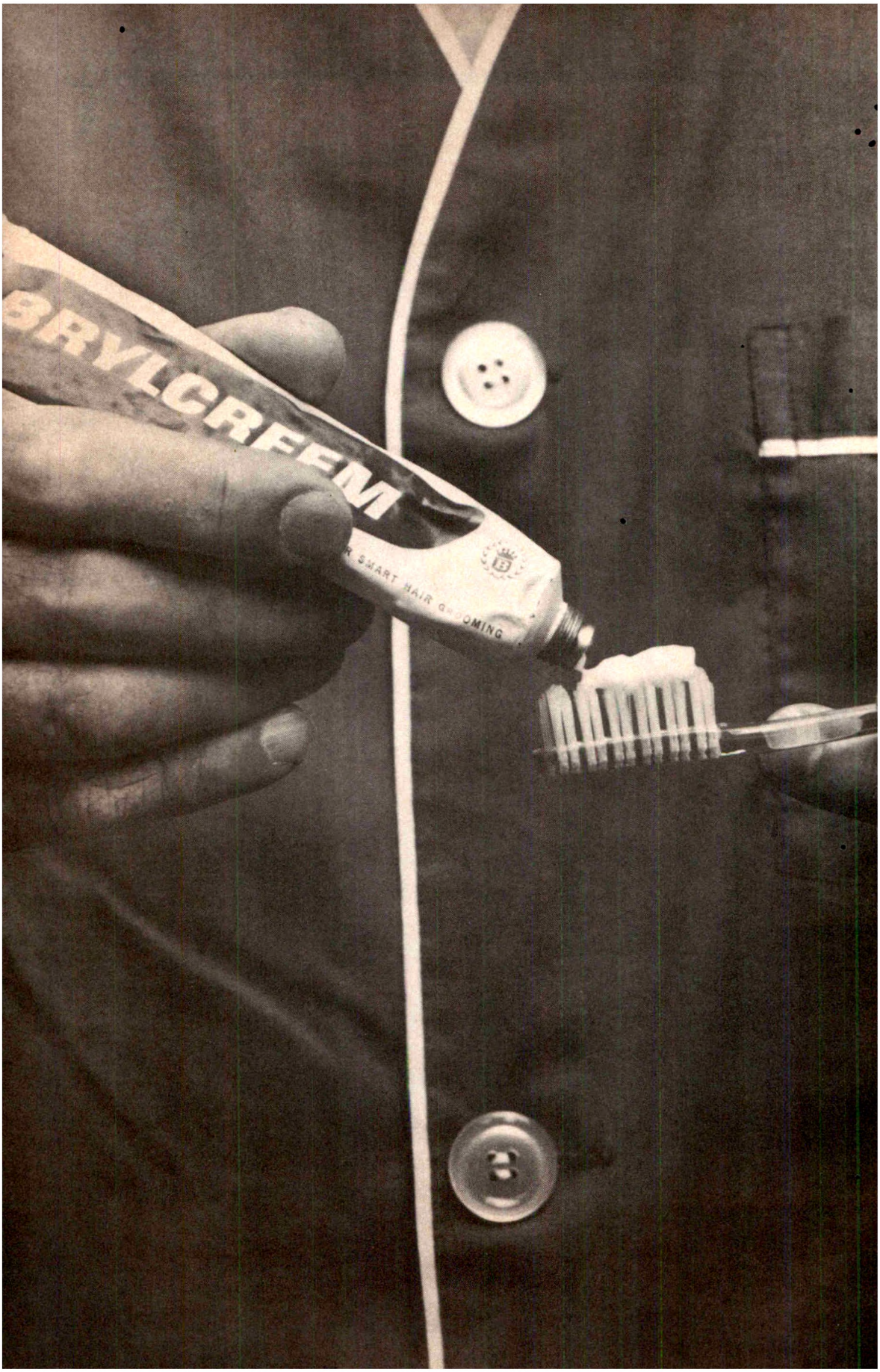
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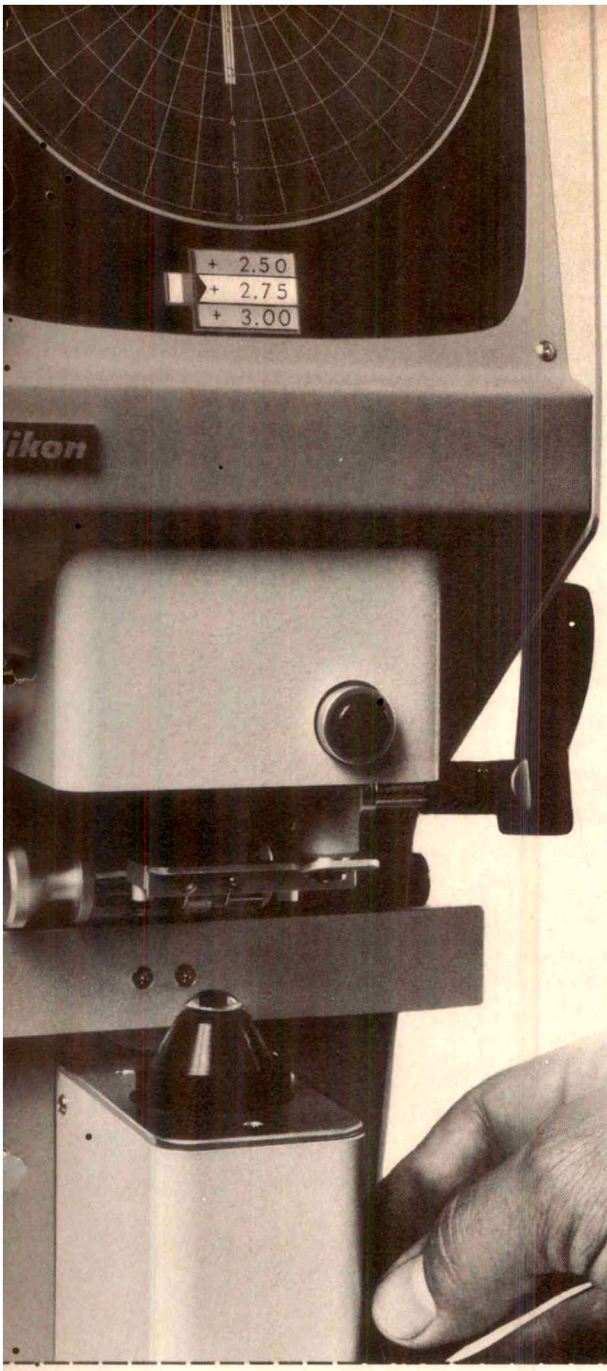
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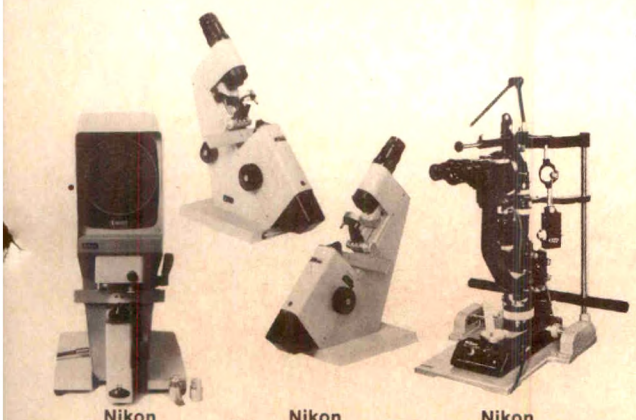
Because of the instrument's vertical configurati you don't have to be a contortionist to check diop value of a lens. Simply blot it, place it on the lens tab and focus the crosslines on the Vertexometer's proj tion screen. Back vertex power automatically appe in numerals in the diopter scale window.

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Write or phone for details on the Vertexometer. Yo find it makes inspection of soft lenses as simple checking glass lenses. We'll also be happy to sup information on our entire line of ophthalmic produc Nikon Inc., Instrument Group, Ophthalmic Div., Ehr reich Photo-Optical Industries, 623 Stewart Aven Garden City, New York 11530. (516) 248-5200.

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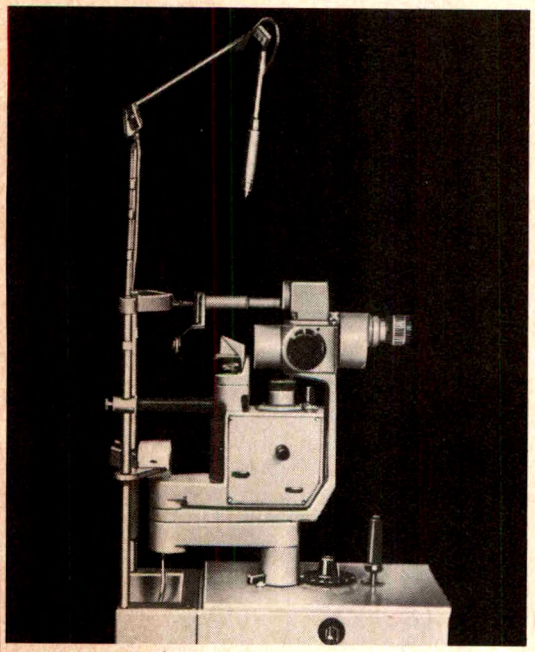
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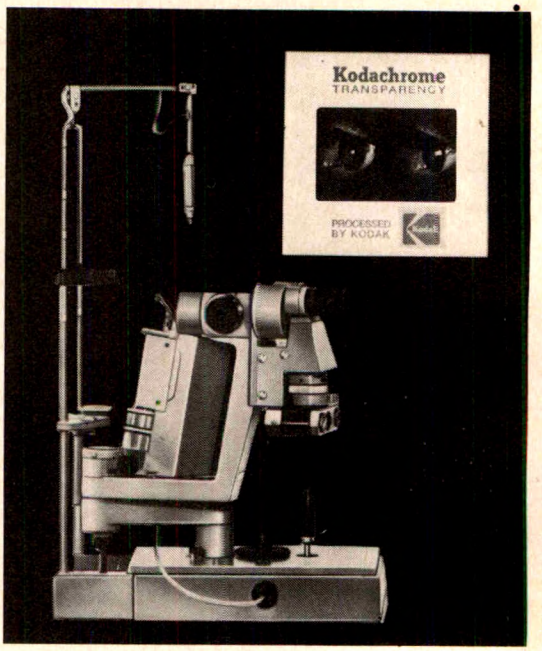
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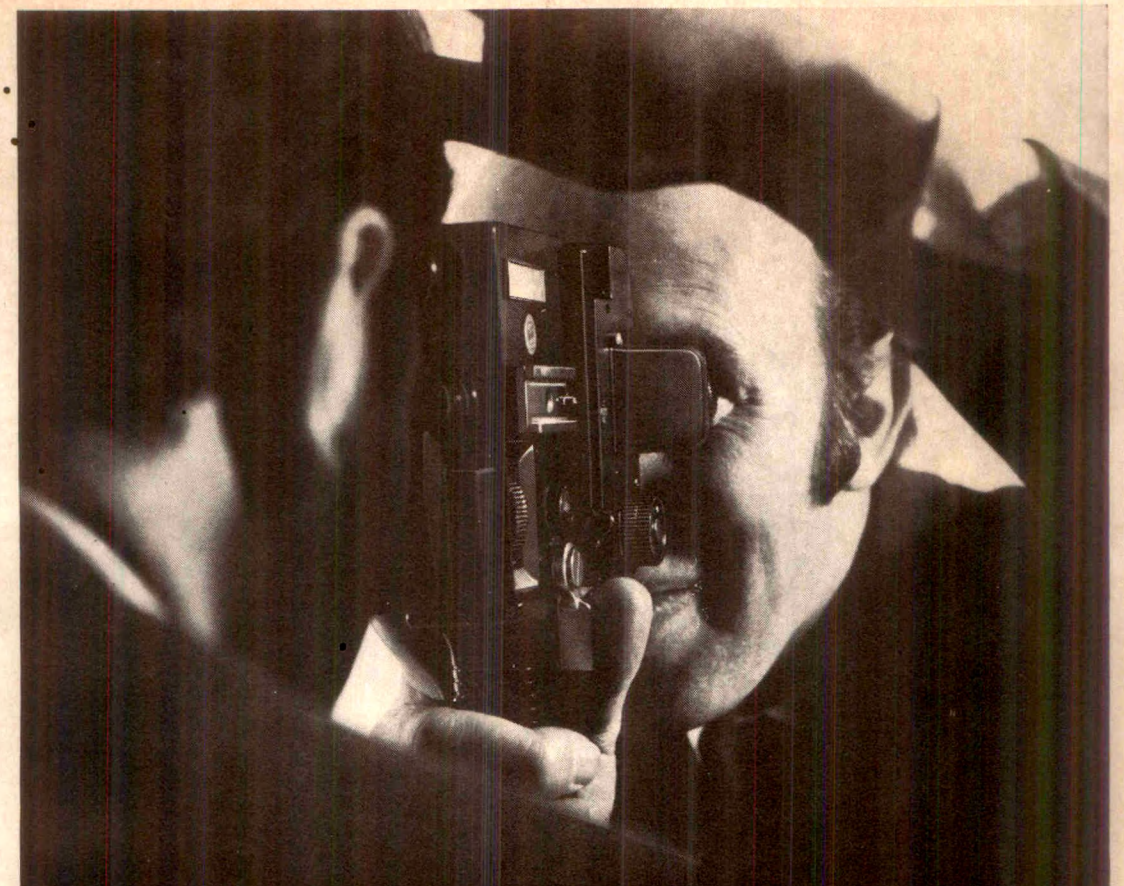
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The Kowa RC-2 Fundus Camera

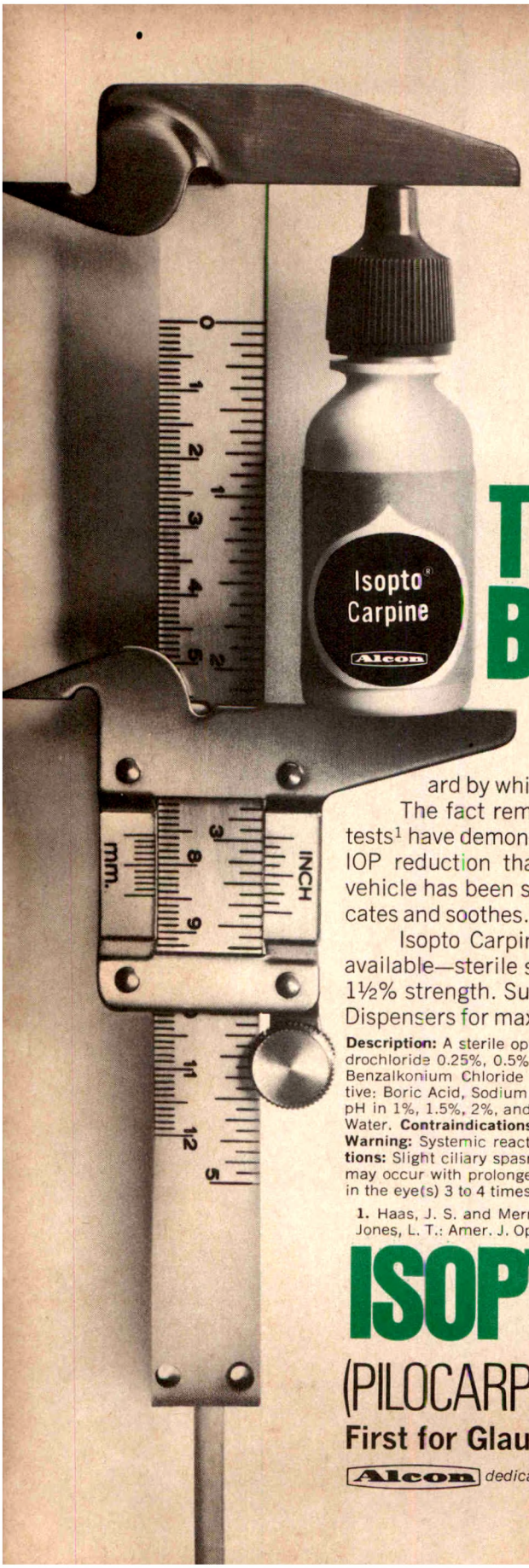
The Kowa RC-2 looks just like a Super-8 home movie camera. It weighs about the same (less than 2¼ pounds) and it's really easy to use. Kowa's advanced technology has made the operation A-B-C simple, but there's no Kindergarten level of sophistication in performance.

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Isopto Carpine comes in the widest range of strengths available—sterile solutions from ¼% to 10%, including a new 1½% strength. Supplied in 15ml and also 30ml Drop-Tainer® Dispensers for maximum economy.

Description: A sterile ophthalmic solution. Each ml contains: Active: Pilocarpine Hydrochloride 0.25%, 0.5%, 1%, 1.5%, 2%, 3%, 4%, 5%, 6%, 8%, or 10%. Preservative: Benzalkonium Chloride 0.01%. Vehicle: Hydroxypropyl Methylcellulose 0.5%. Inactive: Boric Acid, Sodium Chloride in 0.25%, 0.5%, and 1%, Sodium Citrate (to adjust pH in 1%, 1.5%, 2%, and 6%), Citric Acid in 0.25% and 0.5% (to adjust pH), Purified Water. **Contraindications:** When constriction is undesirable such as in acute iritis. **Warning:** Systemic reactions are rare. **Precaution:** Avoid overdosage. **Adverse Reactions:** Slight ciliary spasm with temporary reduction in visual acuity. Contact allergy may occur with prolonged use. Sensitivity is infrequently observed. **Dosage:** 2 drops in the eye(s) 3 to 4 times daily.

1. Haas, J. S. and Merrill, D. L.: Amer. J. Ophthal. 54:21, 1962. **2.** Linn, M. L. and Jones, L. T.: Amer. J. Ophthal. 65:76, 1968.

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AMERICAN JOURNAL OF OPHTHALMOLOGY

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ACUTE MACULAR NEURORETINOPATHY

PIERRE J. M. BOS, M.D.
Amsterdam, The Netherlands

AND

AUGUST F. DEUTMAN, M.D.
Rotterdam, The Netherlands

Recently we observed four women with a peculiar acute macular affection, characterized by slight depression of visual acuity and paracentral scotomas corresponding with dark-reddish, wedge-shaped intraretinal lesions pointing to the fovea.

The macular pigment epithelium appeared normal and the retinal vessels did not show gross abnormalities. The optic disk was unaffected and there were no nerve fiber defects. Visual recovery, when present, progressed slowly over many months.

Since no similar disease process is known to us, we called this entity acute macular neuroretinopathy (neuroepitheliopathy)[1] because of the acute onset and the localization of the lesions in the more superficial retinal layers at the macula.

Two patients were seen in the Amsterdam Eye Clinic, one patient was seen in the Rotterdam Eye Hospital, and the fourth was examined at both hospitals.

Routine ophthalmoscopic examination, fundus photography, and fluorescein angiography were done in all patients. The photographic methods have been described.[2] Kinetic visual fields were recorded with the Goldmann perimeter and static perimetry with the Tübinger perimeter.

From the Department of Ophthalmology, University of Amsterdam (Dr. Bos), and the Eye Hospital, Erasmus, University of Rotterdam (Dr. Deutman), The Netherlands.

Reprint requests to A. F. Deutman, M.D., Department of Ophthalmology, University of Nijmegen, Nijmegen, The Netherlands.

We performed electroretinography and electro-oculography in two patients.[2] All patients underwent general physical examination and laboratory tests.

CASE REPORTS

Case 1—A 29-year-old white woman had noticed black dots and scotomas in both central visual fields since April 15, 1971. The onset of the complaints was sudden. She was first seen on April 20, 1971, when corrected visual acuity in both eyes was 20/20.

Ophthalmologic examination showed no abnormalities outside the macular regions. There were irregular reflexes and dark, brown-reddish flecks in the right macula; some had a triangular configuration with the sharp point of the triangle directed toward the fovea (Fig. 1, left). Some polymorphic spots were present elsewhere in the macula. In her left eye (Fig. 1, right), she demonstrated similar irregular reflexes and some dark red-brownish dots, like those in her right eye.

Biomicroscopy revealed that these spots were not located in the pigment epithelium but in the more superficial retinal structures. Fluorescein angiography was normal (Fig. 2). Kinetic perimetry showed that the peripheral boundaries of the visual fields were intact, while static perimetry demonstrated dense scotomas in the 2- to 5-degree area of both eyes and a slight decrease in central light sensitivity (Fig. 3).

There were no systemic complaints. In her youth the patient had had a splenectomy because of familial thrombocytopenia, but otherwise she had a noncontributory medical history. She was taking the oral contraceptive lynestrenol (Lyndiol).

No subjective changes were observed during follow-up and static visual fields were unchanged. The fundus changes were visible, although the lesions were less obvious.

Case 2—A 33-year-old white woman noticed a scotoma in her left eye of sudden onset on Sept. 18, 1972. Her right eye was completely normal. She had not been ill before the ocular complaints. She had been using lynestrenol for eight years.

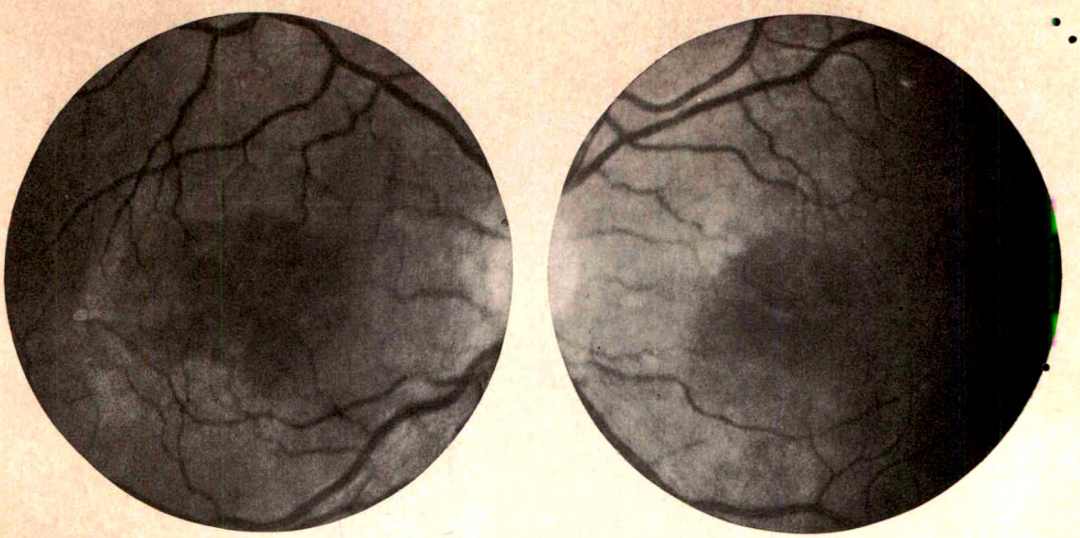


Fig. 1 (Bos and Deutman). Case 1. Right macula (left) and left macula (right) showing darkish wedge-shaped and irregular flecks, localized in the neuroretina.

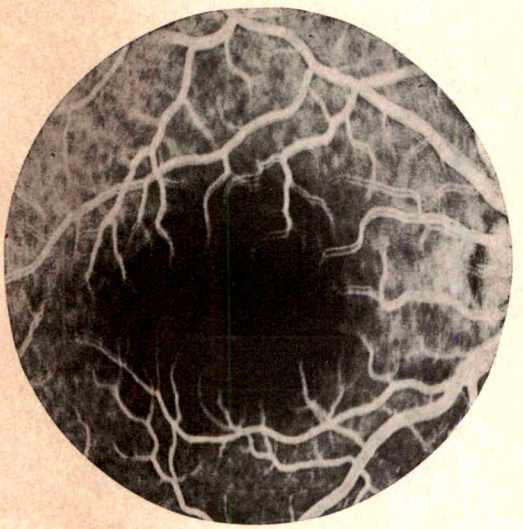


Fig. 2 (Bos and Deutman). Case 1. Fluorescein angiography of the right macula showing a normal fluorescence pattern in the arteriovenous phase.

Two days after the onset of symptoms, she had normal central vision in both eyes. There was a dark brown-reddish spot in the macular region of the left eye close to the fovea (Fig. 4, left). Otherwise her eyes were normal.

Fluorescein angiography revealed some questionably dilated perimacular capillaries (Fig. 4, right). There was, however, no leakage of dye recorded in the late stages of the angiogram, such as seen in cystoid macular edema.[3]

Meticulous static perimetry revealed a scotoma in the 1- to 3-degree area from the center of the left eye (Fig. 5). This scotoma was not as dense as the scotoma recorded in Case 1.

The patient was last seen in October 1973, when the symptoms were unaltered. Careful ophthalmoscopy showed a faint discoloration located where the dark spot was seen originally. Static perimetry still showed a scotoma that had decreased slightly in depth (Fig. 6).

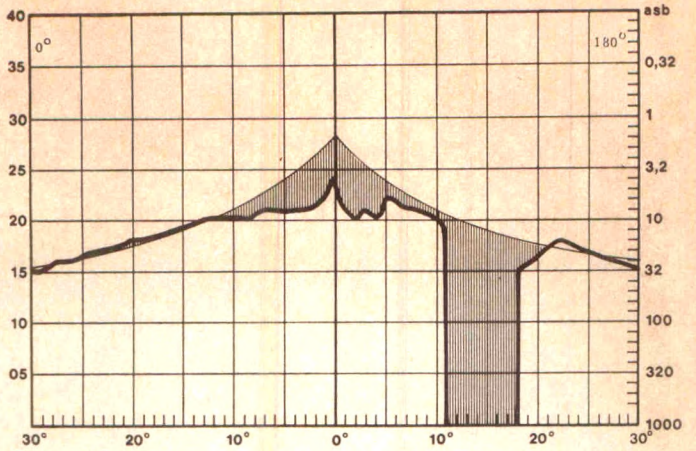
Case 3—A 24-year-old white woman noticed disturbance of her central vision after visiting a game reserve where she had had a bout of enteritis. She claimed she had not been looking at the sun.

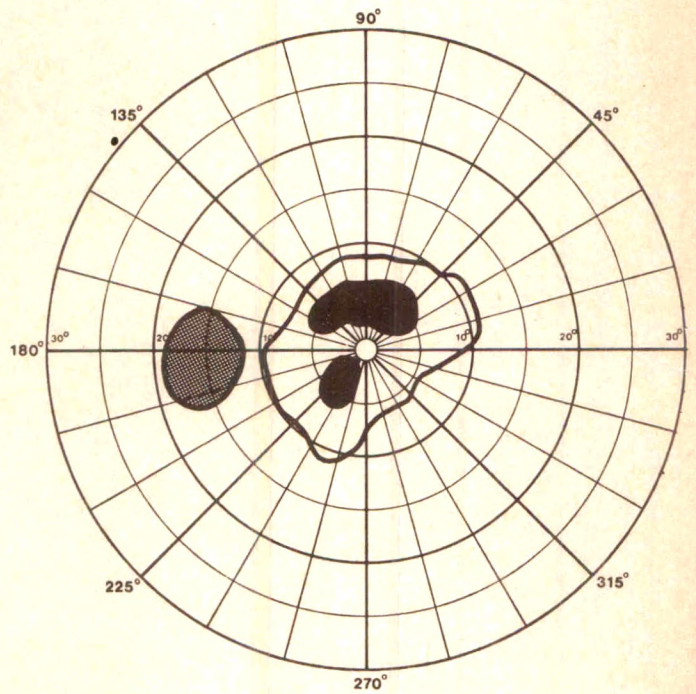
On March 2, 1972, she was seen in the Amsterdam University Clinic. Visual acuity in both eyes was 20/20. Ophthalmologic examination was normal outside the macular regions, which had a swollen glossy appearance with increased reflexes and vague, darkish red, wedge-shaped lesions around the center of the macula. The lesions pointed toward the fovea with a butterfly-shaped appearance (Fig. 7).

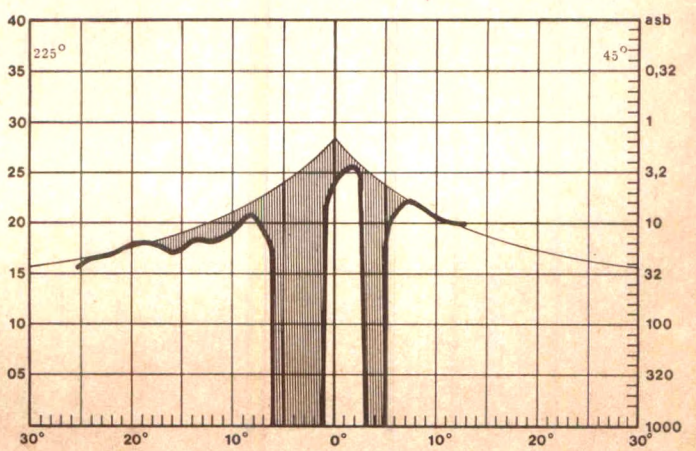
Fluorescein angiography revealed no abnormali-

➤

Fig. 3 (Bos and Deutman). Case 1. Static perimetry (top and bottom) performed with the Tübinger perimeter showing slightly decreased light sensitivity centrally and paracentrally in the right eye (top) and dense paracentral scotomas in the left eye (bottom). These scotomas were also seen with kinetic perimetry (center) in the left eye.


0°
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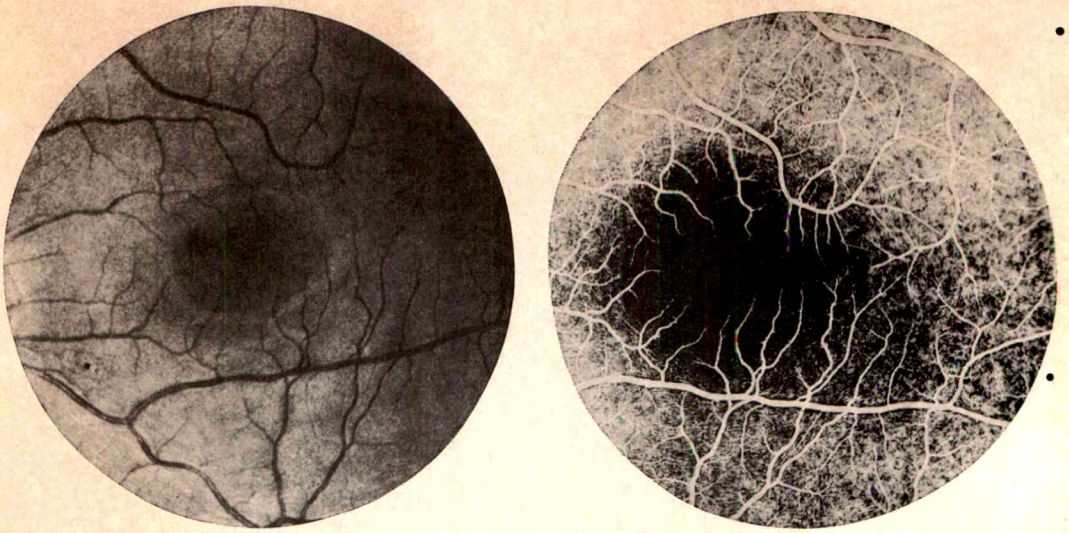


Fig. 4 (Bos and Deutman). Case 2, left eye. Macula showing one darkish, wedge-shaped dot superonasally to the fovea. Fluorescein angiography of this macula (right) showed no clear abnormalities. There is only questionable dilatation of some of the perimacular capillaries.

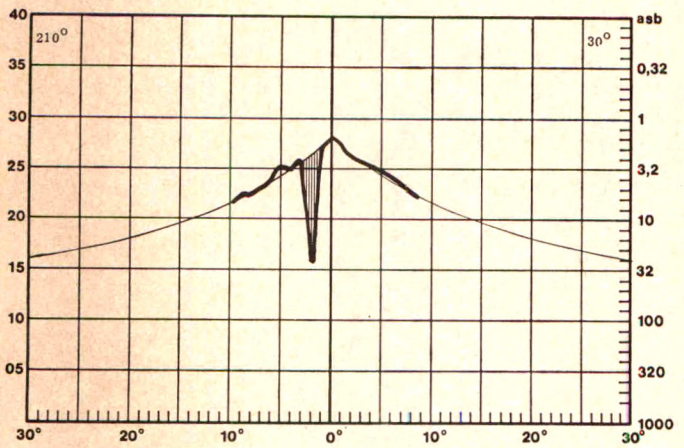


Fig. 5 (Bos and Deutman). Case 2, left eye. September 1972. There is a dense, well-delineated, paracentral scotoma corresponding to the side of the ophthalmoscopically visible dot. This scotoma was recorded with the Tübinger perimeter after painstaking care in static perimetry.

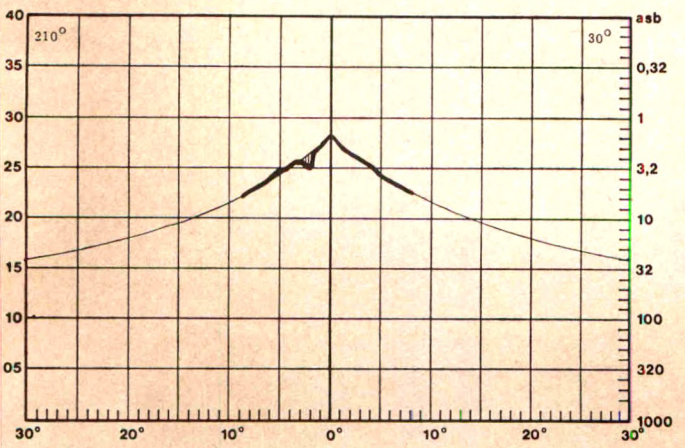


Fig. 6 (Bos and Deutman). Case 2, left eye. May 1973. Left macula showing some remnants of the paracentral scotoma shown in Figure 5.

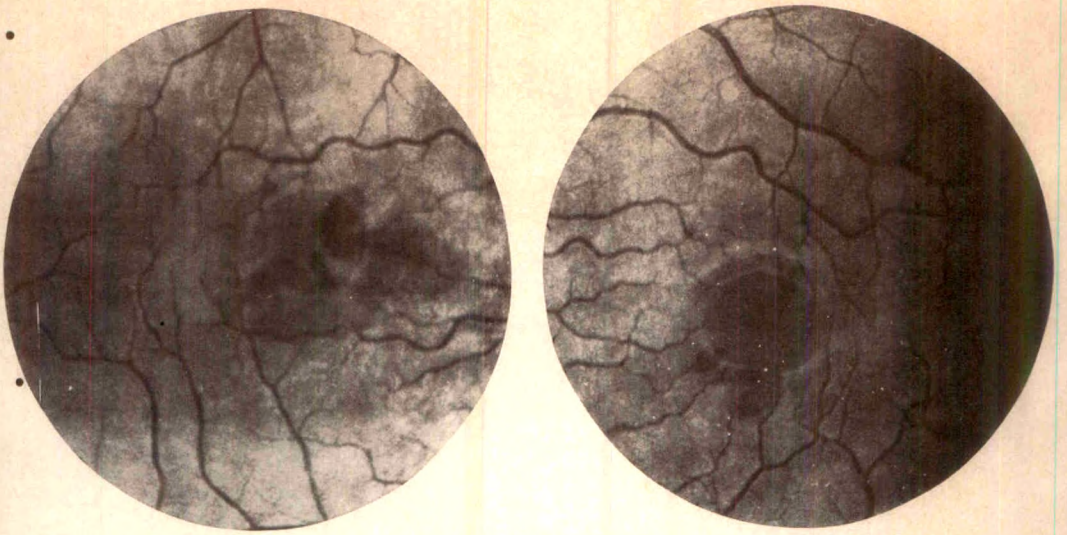


Fig. 7 (Bos and Deutman). Case 3. March 2, 1972. Right macula (left) and left macula (right) demonstrating wedge-shaped lesions not unlike the shape of a butterfly. However, these lesions are localized more superficially in the retina than in butterfly-shaped pigment dystrophy and they are not pigmented.

ties (Fig. 8). Static perimetry, however, showed a paracentral scotoma for maximal luminance above the center in the right eye (Fig. 9). No scotoma was seen in the left eye.

On March 29, she was seen at the Rotterdam Eye Hospital. Visual acuity in both eyes was 20/20. The Amsler grid test showed three small scotomas, two temporal to the fixation point in the left eye. Ophthalmologic examination revealed abnormalities at the macula that appeared swollen and glossy, with increased reflexes and vague, darkish red, wedge-shaped lesions around the center of the macula. The lesions pointed toward the fovea with a butterfly-like appearance. The ophthalmoscopically abnormal areas appeared to correspond almost completely with the scotomas demonstrated on the Amsler grid.

On April 4, 1973, there was little subjective change (Fig. 10). Electroretinography and electro-oculography were performed and appeared to be completely normal. The electroretinogram (ERG) responses were normal. Scotopic and photopic a and b waves were well above the lower limits of normal. The electro-oculogram (EOG) showed a normal light/dark ratio of 2.74 in the right eye and 2.85 in the left eye.

There were no systemic complaints. This patient was taking the oral contraceptive norgestrel (Eugynon).

In October 1973, there were no subjective changes. The same characteristic fundus changes were observed, although they were more faint. Angiography was performed, and was normal. Perimetric details were the same as in March 1972 (Fig. 9).

Case 4—A 32-year-old white woman noticed scotomas in both eyes during a bout of influenza and high fever in the middle of December 1972. When seen on Jan. 2, 1973, visual acuity was R.E.: 20/25, and L.E.: 20/66. Visual acuity in the left eye had always been slightly worse than in her right eye, probably due to amblyopia.

On Jan. 9, her visual acuity was unchanged. The Amsler test demonstrated a paracentral scotoma on the temporal side of the fixation point in the right eye and a rather large scotoma temporal to the center in the left eye. Both macular areas appeared

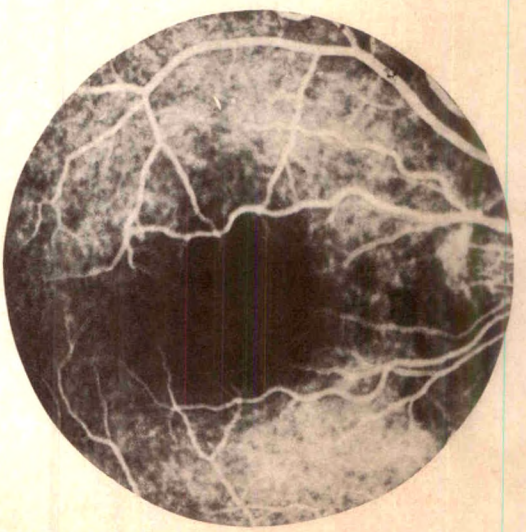


Fig. 8 (Bos and Deutman). Case 3. Fluorescein angiogram of the right macula revealing no abnormalities in the arteriovenous phase.

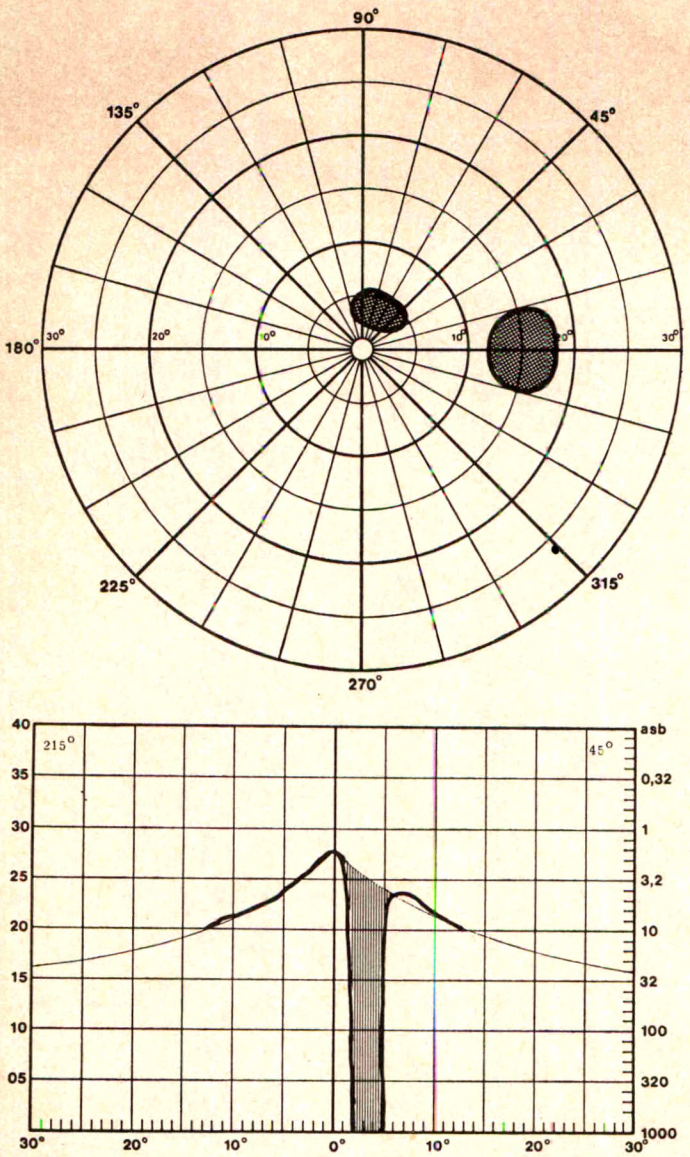


Fig. 9 (Bos and Deutman). Case 3, right eye. Absolute paracentral scotoma in the 45- to 225-degree axis with kinetic perimetry (top) and static perimetry (bottom).

edematous with increased reflexes. There was one dark-reddish, triangular zone in the right macula, just nasal to the foveola (Fig. 11, left), and at least three wedge-shaped darkish-red lesions pointing to the center in the left eye (Fig. 11, right).

The nerve fiber layer was more pronounced nasal to the center. Otherwise the ocular examination showed no pathologic findings. Vessels, disk, and retinal periphery were normal in both eyes and the media were clear.

Fluorescein angiography demonstrated an intact retinal pigment epithelium. There were some questionably dilated perimacular capillaries above the fovea (Fig. 12, top left), but there were no fluorescein leaks (Fig. 12, top right and bottom left).

With the Goldmann contact lens, the retinal swelling appeared to be localized to the inner portion of the sensory retina. The patient was hospitalized on Jan. 16, when vision had not improved. A general physical and laboratory examination revealed a slightly abnormal glucose tolerance test. There was no glycosuria. She had hypercholesterolemia (9.9 mM/1; normal, 6.4 mM/1). She had used contraceptives for many years. The patient

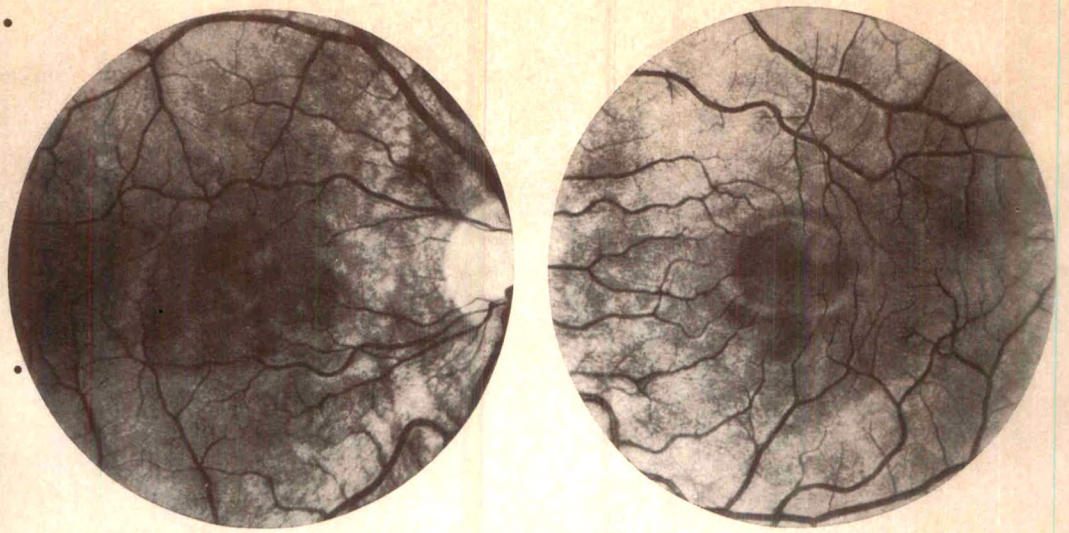


Fig. 10 (Bos and Deutman). Case 3. April 4, 1973. Right macula (left) and left macula (right) with the wedge-shaped paracentral dots that are more visible in tht right eye than in the left eye.

received one tablet of xanthinol niacinate (Complamine), twice daily, carbon dioxide inhalation, clofibrate capsules, and a diet. A neurologic examination, including x-ray films of the sella turcica, was normal.

On Jan. 18, central visual fields showed a small paracentral scotoma on the superotemporal side of the fixation (Fig. 13). On Jan. 29, visual fields were unchanged, but by May 11, there was a small but definite decrease in the size and depth of the scotomas (Fig. 14).

Electroretinograms performed on Jan. 17, with diffuse and macular stimulation, were normal. The visually evoked cortical potentials were also normal.

On May 4, visual acuity was R.E.: 20/25, and L.E.: 20/50. Subjectively there was not much change, although the left eye had improved slightly.

On June 27, visual acuity was R.E.: 20/22, and L.E.: 20/40. She complained of seeing flecks close to the center in the right eye and paracentral and temporal flecks in the left eye. The maculae appeared swollen although the swelling had subsided.

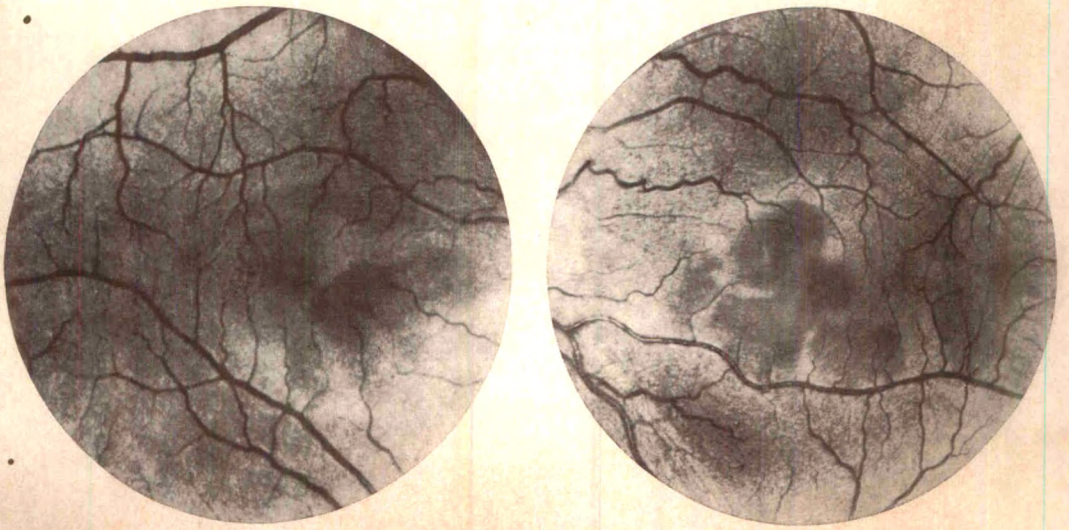


Fig. 11 (Bos and Deutman). Case 4. Acute macular neuroretinopathy. Clearly visible darkish wedge-shaped lesions are in the superficial part of the retina. In the left eye (right), these lesions are cloverleaf shaped and the nerve fiber layer demonstrates an increased visibility.

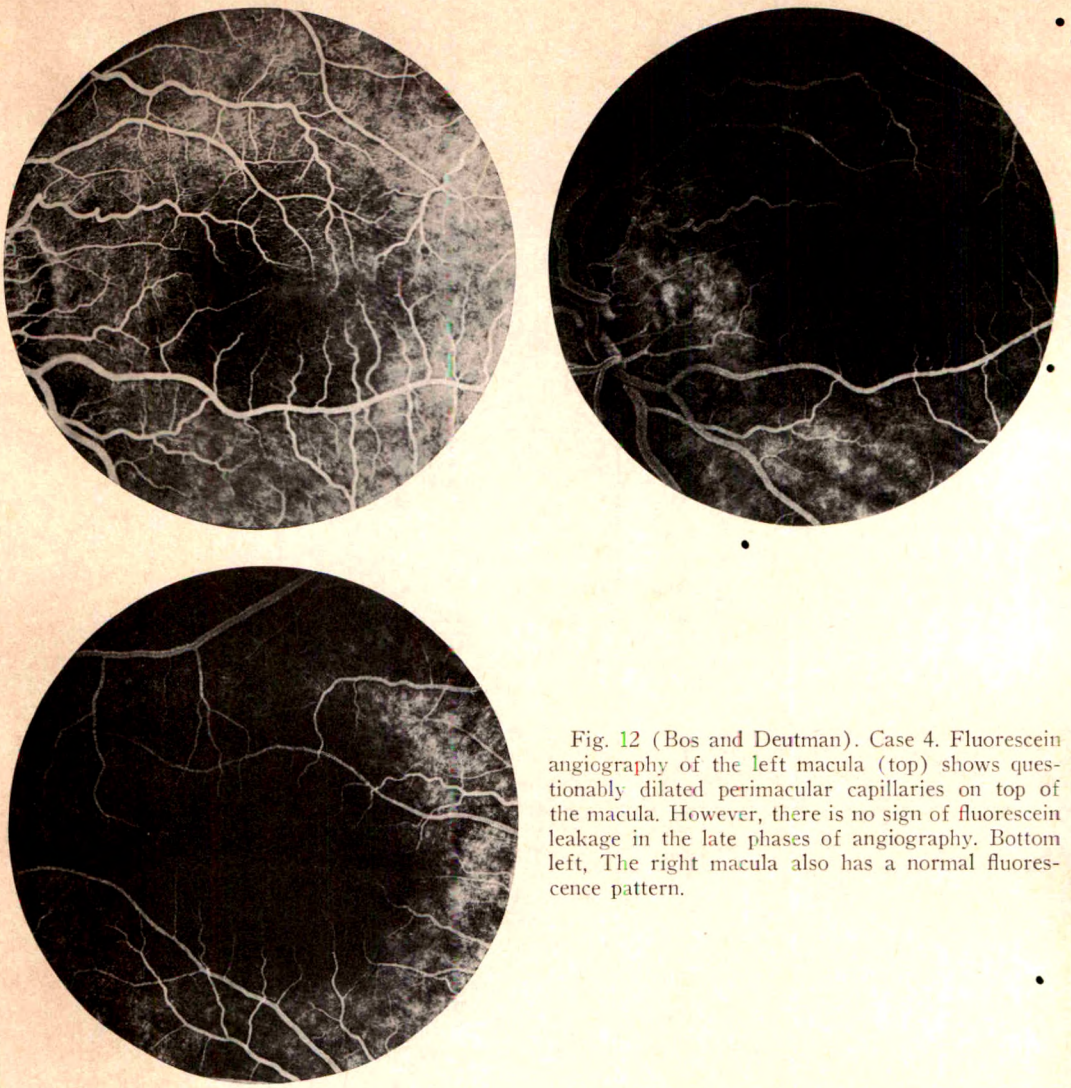


Fig. 12 (Bos and Deutman). Case 4. Fluorescein angiography of the left macula (top) shows questionably dilated perimacular capillaries on top of the macula. However, there is no sign of fluorescein leakage in the late phases of angiography. Bottom left, The right macula also has a normal fluorescence pattern.

On Nov. 19, visual acuity was R.E.: 20/20, and L.E.: 20/33. The paracentral scotomas were present and caused considerable disability.

Discussion

This disease appears to be a distinct entity that, to our knowledge, was described only in a short communication.[1]

It is different from the many clinical diseases affecting the central fundus, recognized in recent years and differentiated from one another based on the nature of the disease and the accompanying morphologic changes.

Central serous choroidopathy[4] is one such entity that is well known but poorly understood. It is probably caused by dilation and profusely leaking capillaries of the central choriocapillaris.

Acute posterior multifocal placoid pigment epitheliopathy is another of these entities.[5] Although some authors[5] think this disease process is due to pigment epithelial disease, there are arguments in favor of a primary affection of the choriocapillaris.[6] In both diseases the morphologic changes occurring in the pigment epithelium are probably secondary.

The changes in acute retinal pigment epi-

theliitis[7,8] appear to be nearly completely restricted to the pigment epithelium and this disease has a more favorable course, leading to complete recovery in six to ten weeks. There are no cells in the vitreous body or in the anterior chamber. A viral inflammation probably causes this self-limiting condition.

Serpiginous (geographic) choroiditis[1,9] presents lesions at different stages of evolution. In early lesions there is a definite pale swelling of the pigment epithelium while older lesions demonstrate atrophy of the pigment epithelium and choriocapillaris surrounded by an edematous retinal zone. This inflammatory disease is characterized by relentless progression, presents in patients in their fourth decade and, in our experience, responds well to corticosteroids.

The so-called presumed histoplasmic choroiditis represents a distinct clinical entity

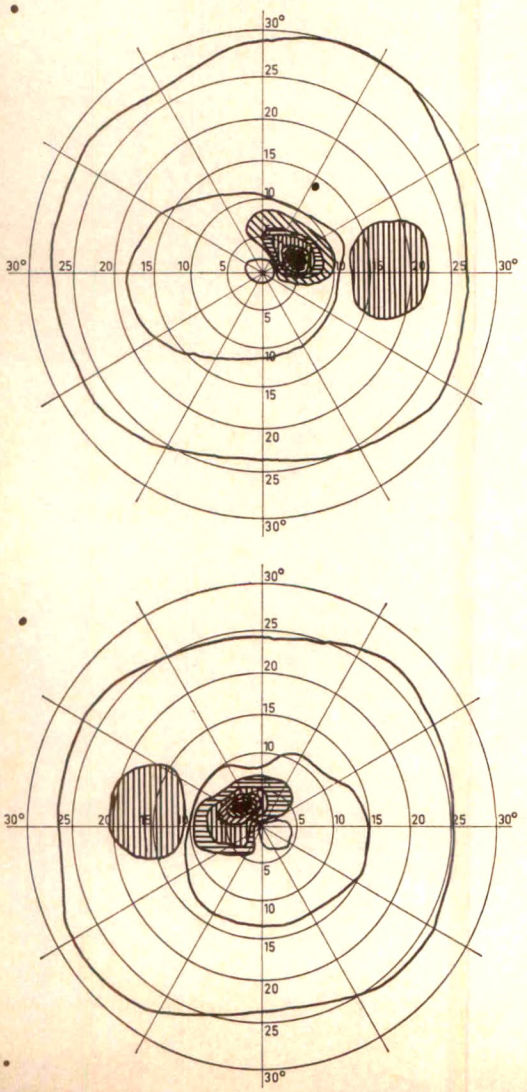


Fig. 13 (Bos and Deutman). Case 4. January 1973. Central visual fields demonstrating dense paracentral scotomas on the superonasal side of the center. Top, right eye; bottom, left eye.

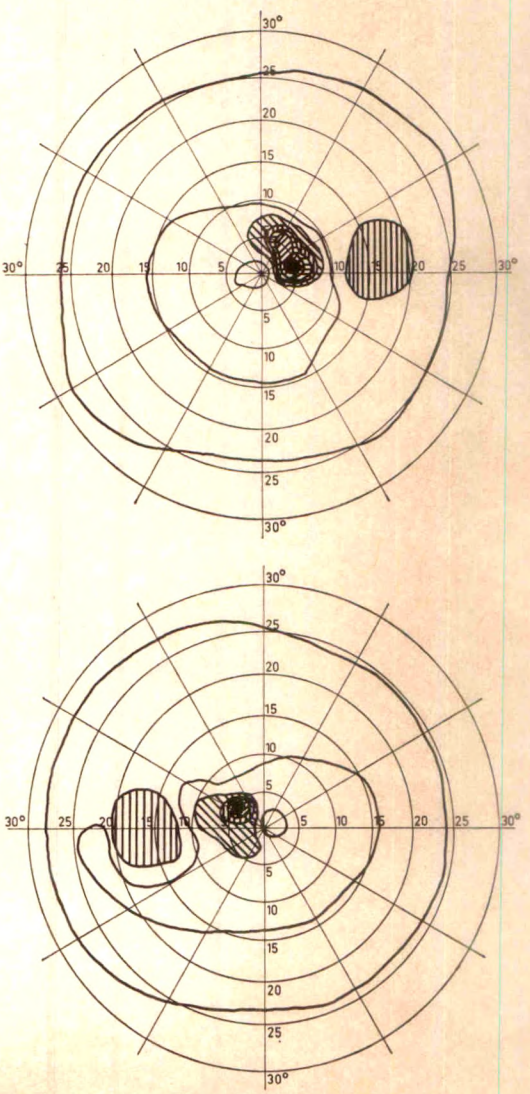


Fig. 14 (Bos and Deutman). Case 4. May 1973. Central visual fields demonstrating some improvement. The scotomas are slightly smaller and less dense than in January 1973. Top, right eye; bottom, left eye.

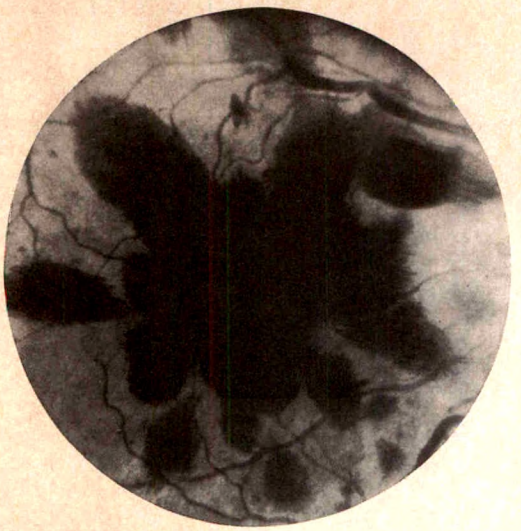


Fig. 15 (Bos and Deutman). Case 4. Wedge-shaped lesions, shaped not unlike the lesion in acute macular neuroretinopathy, in a patient with intraretinal hemorrhages due to hypertensive retinopathy.

affecting adults, characterized by subretinal neovascularization at the fovea. We saw this ocular syndrome in patients without evidence of previous infection by *Histoplasma capsulatum.*[1]

The disease we present appears to be localized to the more superficial retinal layers, shown well on binocular slit-lamp examination, while fluorescein angiography displayed no choroidal or retinal pigment epithelial abnormalities. The retinal vessels do not show definite abnormalities and do not leak fluorescein. The nerve fiber layer is not obviously affected since no nerve fiber layer defects were disclosed even after extensive perimetric examination.

There was no diffuse retinal disturbance since, in those patients tested, the ERGs and EOGs were normal. Static perimetry demonstrated a well-localized paracentral retinal disease with dense scotomas. The lesions were located predominantly on the nasal side of the fovea. The wedge-shaped lesions were shaped not unlike certain intraretinal hemorrhages (Fig. 15) and, therefore, may be localized at the same level in the neuroretina.

As in all macular diseases without striking ophthalmoscopic changes, optic neuropathy has to be differentiated. However, there are no macular changes in optic neuropathy and partial or complete optic atrophy occurs in time. The visual fields and the macular changes together with the normal appearance of the optic disk indicated macular pathology in all four cases. In Case 4, optic nerve pathology was excluded by normal, visually evoked cortical potentials and by a normal neurologic examination.

Addendum—Recently one of us (P.J.M.B.) examined a 30-year-old white woman who developed acute macular neuroretinopathy a few weeks after an influenza-like disease. Visual acuity was R.E.: 20/20, and L.E.: 20/100. The maculae showed wedge-shaped lesions in the superficial retinal layers (Fig. 16). Paracentral scotomas were elicited. Color vision was normal. After a few weeks visual acuity was 20/20 in both eyes. However, four months after the visual symptoms started, she still had paracentral scotomas. No systemic abnormalities were found. This patient used the oral contraceptive ethinyl estradiol (Neogynon).

Another patient, a 23-year-old white man who developed visual problems in his right eye after a bout of influenza, presented with a mild form of acute macular neuroepitheliopathy. Visual acuity was R.E.: 20/25, and L.E.: 20/20. Nasally to the right fovea there was a darkish dot in the superficial retinal layers (Fig. 17). Fluorescein angiography did not show any abnormality. Color vision was also normal. Perimetry, however, demonstrated a small and dense visual field defect at the site of the ophthalmoscopically visual lesion. The left eye was completely normal. The macular picture did not change during two months of observation.

Summary

An unrecognized acute macular affection occurred in four women, 24 to 35 years old, using oral contraceptives who com-

plained of a sudden decrease of visual acuity or paracentral scotomas.

Three patients had bilateral lesions and one patient had unilateral lesions. These lesions consisted of darkish brown-red, wedge-shaped dots in the macula pointing to the fovea. These dots were located mostly on the nasal side of the macula.

Biomicroscopy showed these lesions were located in the superficial layers of the retina.

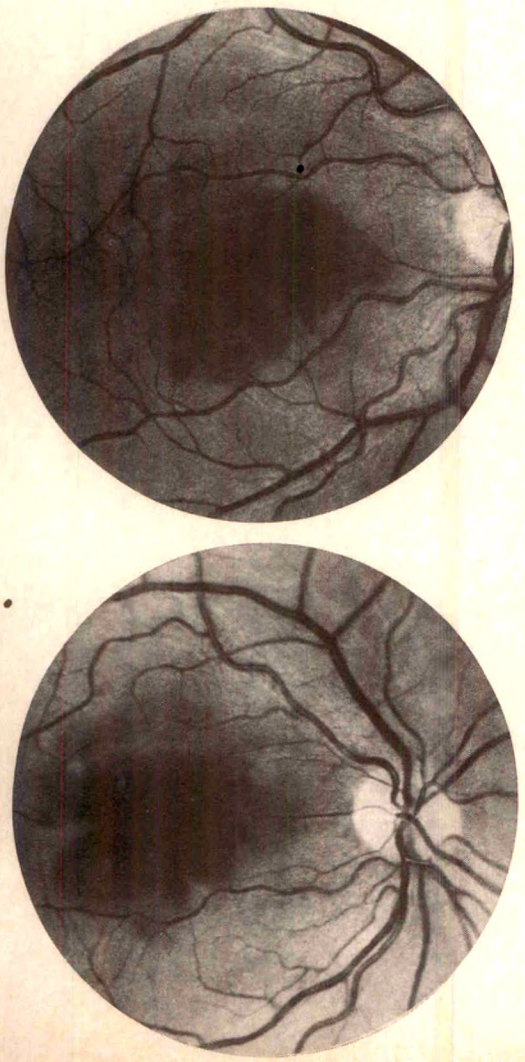


Fig. 16 (Bos and Deutman). Right and left macula (top and bottom, respectively) of a 30-year-old white woman shows the typical superficial wedge-shaped lesions of acute macular neuroretinopathy. The wedges point to the center of the fovea.

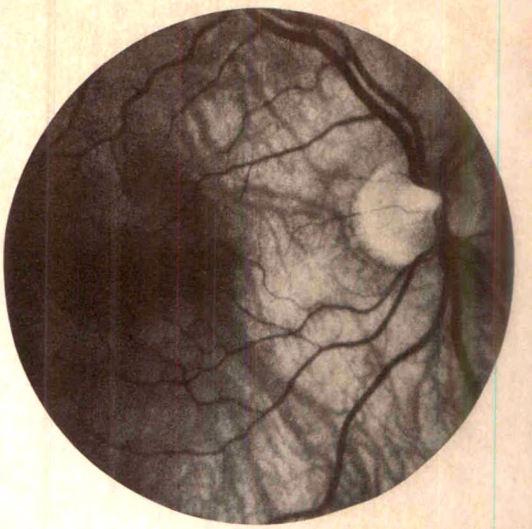


Fig. 17 (Bos and Deutman). A small darkish dot on the nasal side of the right fovea corresponding with a deep paracentral scotoma as the only manifestation of acute macular neuroretinopathy.

The retinal vessels, pigment epithelium, and optic disk showed no distinct pathologic features. Fluorescein angiography, performed repeatedly, showed some questionably dilated perimacular capillaries without leakage in two cases.

Static perimetry delineated dense paracentral scotomas. Recovery was slow or absent, confirmed by perimetric observation.

Ophthalmoscopic, fluorescein angiography, and perimetric details excluded an affection of the pigment epithelium, the nerve fiber layer, and the optic disk. Since the affection appears to be localized superficially in the retina, we called this specific entity acute macular neuroretinopathy.

ACKNOWLEDGMENTS

H. H. A. Hötte, M.D., and R. A. Crone, Ph.D., referred Case 3, and H. E. Henkes, Ph.D., referred Case 4.

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Ophthalmic miniature

He had only one good eye. The left distinguished only light and shade. But the good eye was dark-bright, full of observation through the overhanging hair of the brow as in some breeds of dog. For his height he had a small face. The combination made him conspicuous.

Saul Bellow, *Mister Sammler's Planet*
New York, Viking Press, 1970

PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA ASSOCIATED WITH RETINAL PIGMENT EPITHELIOPATHY

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Perugia, Italy

Progressive external ophthalmoplegia is a syndrome characterized by occurrence in either sex at any age, most frequently during the second decade, by slow progression, and bilateral weakness of the extraocular muscles of each eye. The levator palpebrae superioris muscles rarely are solely affected. The condition is inherited as an autosomal dominant trait with incomplete penetrance.

Progressive external ophthalmoplegia may be associated with other pathologic conditions, such as hypogonadism,[1] cerebellar ataxia,[2] cardiopathy,[3] spastic tetraparesis,[4] anal sphincter insufficiency,[5] and retinal pigmentary dystrophy. Forty-two cases of progressive external ophthalmoplegia associated with pigmentary dystrophy of the retina have been described.[6–28]

We document an additional case of progressive external ophthalmoplegia associated with atypical retinal dystrophy that we studied in detail, principally by means of retinal fluorescein angiography.

CASE REPORT

A 20-year-old man had no family history of neuromuscular or eye disease. At 11 years of age, he developed progressive bilateral blepharoptosis. He was underweight and underdeveloped. There was marked, slightly asymmetrical bilateral blepharoptosis with secondary frontalis musculature compensatory overaction. Movements of both eyes were severely limited, particularly on upward gaze. The face was hypomimic. The musculature of the head, neck, and upper half of the trunk (Fig. 1) was thin.

Slight hypotonia, hyposthenia, and proprioceptive hyporeflexia were observed. The lower limbs and gait were normal. There was neither ataxia nor cerebellar or pyramidal signs. The intelligence quotient was 82.

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Visual acuity was 20/20 in each eye. The pupils were normal. Visual fields were normal. On ophthalmoscopic examination, the optic disk and the caliber of the retinal vessels appeared to be normal. There was a nasal peripapillary crescent of atrophic pigment epithelium. The maculae, particularly the left, had a slight salt-and-pepper appearance but no pigment clumping was present (Fig. 2). On red-free ophthalmoscopy, there seemed to be some depigmentation of the retinal pigment epithelium, particularly in the peripapillary areas. Laboratory studies of the blood and urine, skull and chest x-ray films, and electroencephalography revealed no abnormalities.

RESULTS

Electromyography—In the concentric needle electrode examination of eye, face, neck, shoulder, and limb muscles, there was no resting activity in any muscle. Voluntary



Fig. 1 (Daniele, Cianchetti, and Cao). Ocular myopathy. Note the thin musculature of the head and neck, the hypomimic face, and bilateral blepharoptosis. Impairment of the extraocular movements was marked.



Fig. 2 (Daniele, Cianchetti, and Cao). Ophthalmoscopic aspect of the fundus of the left eye showing a temporal crescent of peripapillary atrophy. The diffuse abnormality of the pigment epithelium is not prominent. There is clumping of dustlike pigment in the macular area.

activity was not detectable from the left superior rectus muscle. The left levator palpebrae superioris muscle showed a variable pattern, slightly reduced in some detection areas (Fig. 3, a), but near to interference in others (Fig. 3, b), contrasting with the almost missing eyelid elevation; there was low amplitude, and spikes were frequently irregular.

There were interference and subinterference patterns with short and irregular potentials in the left orbicularis oculi muscle, left sternocleidomastoideus muscle, and left and right deltoideus muscles (Fig. 3, c and d). There were fewer abnormalities in the right palmaris magnus muscle and the right and left adductor pollicis muscles; the right tibialis anterior muscle was normal.

Maximal motor conduction of the ulnar and median nerves was normal. Tetanic stimulation was 50 c/sec, and Desmedt's test showed no changes in the amplitude of the evoked potentials in the ulnar nerve with detection from the adductor pollicis muscle.

There was primary myopathy with maximum severity in the extraocular muscles (loss of parenchyma in the superior rectus muscle, followed by parenchymal loss in the muscles of the face, neck, and shoulders). The following studies showed normal or negative values: prostigmine test (2 mg intramuscularly), dark adaptation, Farnsworth-100 color vision hue test, electroretinogram (b-wave, −0.35 mV), and an electro-oculogram.

Retinal fluorescein angiography—Angiograms disclosed clear signs of alterations in the entire pigment epithelial layer, signs not seen ophthalmoscopically. The most precocious finding was an early, diffuse choroidal hyperfluorescence, more marked

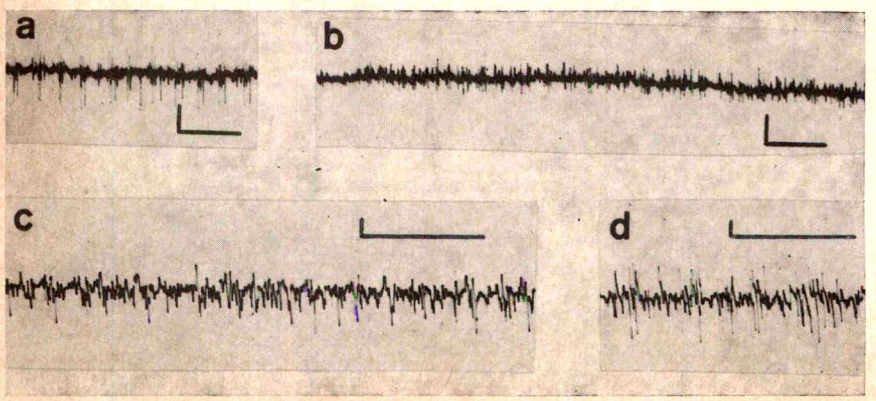


Fig. 3 (Daniele, Cianchetti, and Cao). The electromyograph of the left levator palpebrae muscle was slightly reduced (a) in some detection areas but near to interference (b) in others (0.1 mV/100 msec). Interference and subinterference patterns (c and d) had short and irregular potentials in the left orbicularis oculi muscle, left sternocleidomastoideus muscle, and left and right deltoideus muscles (0.2 mV/100 msec).

along the main retinal vessels whose caliber appeared to be normal. The underlying choroidal and retinal circulation appeared normal.

There was general thinning of the pigment epithelium with a nasal peripapillary area of atrophy, and widespread patches of rarefaction that revealed multiple, discrete, nonleaking areas of hyperfluorescence due to a reduced filter effect of the pigment layer. These hyperfluorescent areas remained constant in size and configuration, varying only in brightness throughout the angiography study.

The fluorescence observed earlier in the retinal arterial phase persisted beyond the retinal venous phase of angiography. The filter effect was almost lost in the macular area. A long-lasting scleral fluorescence persisted abnormally. The findings were similar in each eye (Fig. 4).

Discussion

Our patient belongs to the group of uncommon cases of progressive external ophthalmoplegia associated with pigment dystrophy of the retina. Electromyography diagnosed an ocular myopathy that extended to the muscles of the face, neck, and shoulder girdle. Normal values of muscle enzymes in blood serum are compatible with slowly progressive disease and limited extension of macular changes.[29]

In the cases that have been reported, retinal changes have always been described as forms of "atypical" retinal pigment dys-

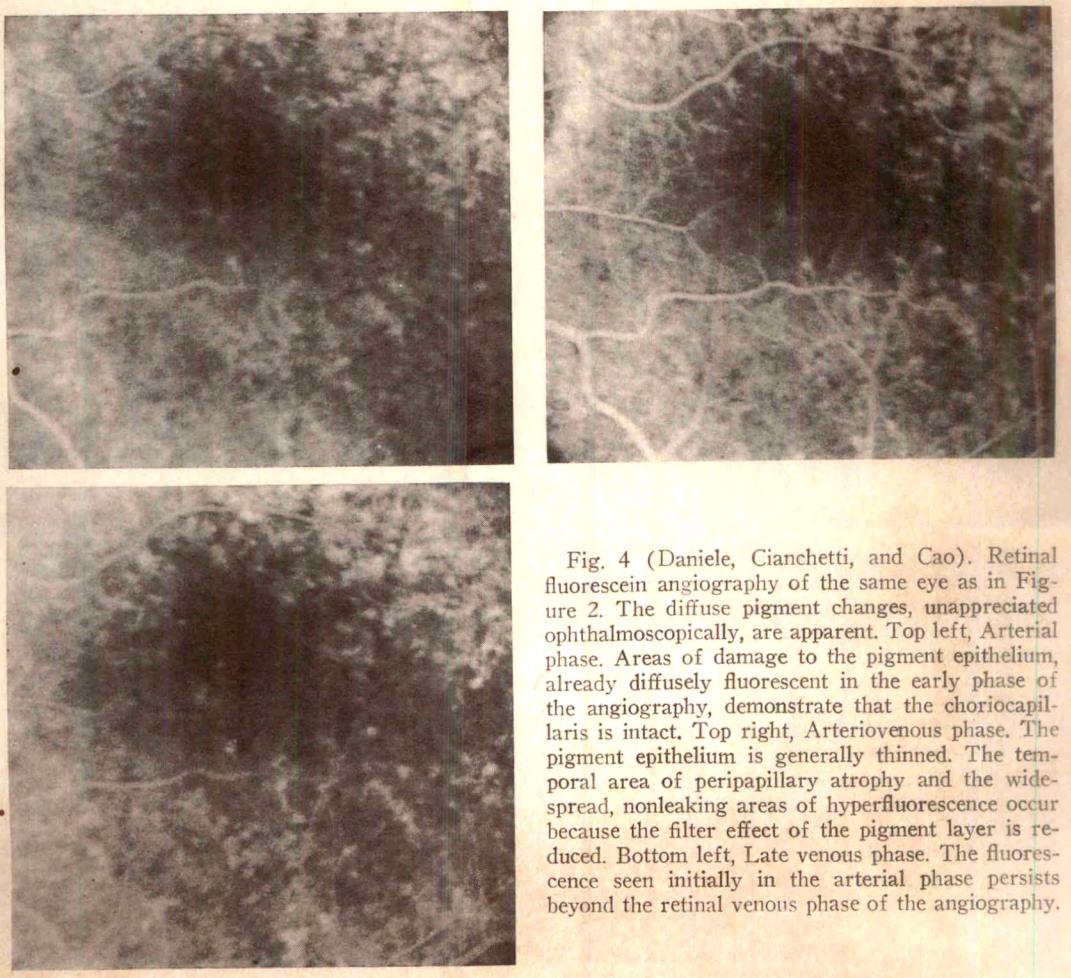


Fig. 4 (Daniele, Cianchetti, and Cao). Retinal fluorescein angiography of the same eye as in Figure 2. The diffuse pigment changes, unappreciated ophthalmoscopically, are apparent. Top left, Arterial phase. Areas of damage to the pigment epithelium, already diffusely fluorescent in the early phase of the angiography, demonstrate that the choriocapillaris is intact. Top right, Arteriovenous phase. The pigment epithelium is generally thinned. The temporal area of peripapillary atrophy and the widespread, nonleaking areas of hyperfluorescence occur because the filter effect of the pigment layer is reduced. Bottom left, Late venous phase. The fluorescence seen initially in the arterial phase persists beyond the retinal venous phase of the angiography.

trophy, characterized by good visual function, absence of optic atrophy, and attenuation of the retinal vessels. However, there has been heterogeneity of the ophthalmoscopic findings, similar to but never specific for retinitis pigmentosa. The reported findings vary in fact from those found in classic tapetoretinal bone-corpuscle pigmentation to granular, clumped, or fine dustlike pigmentary disturbances detectable at the posterior pole, at the equator, or in the extreme periphery of the fundus. In other words, a case of true tapetoretinal degeneration associated with ocular myopathy has not been reported to our knowledge. Even in Kearns's[21] patient, the only case studied histopathologically, the diagnosis of retinitis pigmentosa was impossible. Prior reports never considered the appearance of the fundus other than the contextual retinal alterations that manifested generalized abiotrophic processes of ocular myopathy.[13,15,19,30]

The suggested diagnosis of primary retinal pigment epitheliopathy in our case is supported by: (1) the lasting normality of the retinal function. The integrity of the peripheral neurons and of the neuroepithelium persisted despite the progressive worsening of the function of the muscles affected by the degenerative process; and (2) the findings of retinal fluorescein angiography. When histologic study is impossible, retinal angiography discloses the extent and severity of the abiotrophic or degenerative changes, unappreciated or misinterpreted by ophthalmoscopy.

In our patient, the early fluorescence present in the arterial phase and persisting beyond the venous phase without changing size indicated a defective pigment epithelium rather than a leakage.

When the patient was examined ophthalmoscopically, even with red-free light, the less-extended visible changes were fewer than with fluorescein angiography. The changes seemed to spread all over the fundus, diffuse beyond the ophthalmoscopic limits, giving the impression of a global process. This discrepancy is an angiographic peculiarity of the pigment epitheliopathies alone.[31,32] When the choriocapillaris or Bruch's membrane are affected, a more precise regional topography, more irregular borders, and dense and localized plaques of hyperfluorescence characterize the fundus changes. It is more difficult in the case of pigment epitheliopathy to establish whether the background mottling of the fundus is due to increased transparency of the altered pigment epithelium or to impregnation of the pigment cells by the stain. Pigment epithelium is not just a simple support for the photoreceptors or a filter for the light energy required by the photoreceptors. It is a layer of complex cells whose specific functions include transmission of nutrients from the choriocapillaris to other parts of the retina, storage of vitamin A and its conversion to forms suitable for the synthesis of rhodopsin, some mucoprotein synthesis, phagocitosis, and digestion of the rod-segment disks and of other substances from the neuroretina.[33-38]

Failure of the pigment epithelium to function properly is responsible for some types of maculopathies, as well as changes in Bruch's membrane secondary to disease of the pigment epithelium that augments the progress of retinal degeneration.[39] Fundus flavimaculatus and Best's or Stargardt's disease are caused by damage of the retinal pigment epithelium, probably due to a failure of the enzymatic system within the pigment cells.[31,40,41] According to Klien and Krill,[31] fundus flavimaculatus, a retinal affection whose fluorescein angiographic features resemble those of our case, should be considered the consequence of a genetic disorder responsible for a primary defect in the pigment epithelium. Rodrigues and associates'[42] report of a case of defective pigment epithelium alone in a boy with a trisomy-18 syndrome adds interest to the observation of interrelationship between genetic disorders and retinal changes confined to the pigment layer alone.

These findings suggest that the atypical forms of retinal dystrophies associated with

ocular myopathy could be clinical expressions of a unique, original genetic defect confined to the pigment epithelium layer. This view is supported by Gass's[43] report of a 16-year-old girl with Kearns-Sayre syndrome who revealed definite but not ophthalmoscopically prominent alterations of the pigment layer, exactly as those that occurred in our patient. Therefore, there is no relationship between true retinitis pigmentosa and primary retinal pigment epitheliopathy in the course of ocular myopathy since histopathologic studies of retinitis pigmentosa indicate that the first step in the dystrophic process is always a primary degeneration of the photoreceptors.[44] Further anatomic and functional changes follow thereafter.

The most likely explanation for damage to the pigment epithelium during the course of ocular myopathy is that the muscular dystrophy gene has pleiotropic effects or different degrees of penetrance. In addition to the effect on the muscle tissue, primary or secondary biochemical changes could damage the development and functions of the retinal pigment epithelium. Depending on the severity and extent of the original damage to the epithelial cells, retinal changes can follow the primary epitheliopathy and account for the atypical and irregular disorders so far reported. Even though narrowing of the vessels and pallor of the optic disk may occasionally be present, such functional disturbances as hemeralopia, dischromatopsia, annular scotomas, or peripheral contraction of the visual fields, which always characterize the true tapetoretinal degenerations, are practically absent in the retinal alterations associated with ocular myopathy.[45]

Summary

The diagnosis of ocular myopathy associated with a primary retinal pigment epitheliopathy in a 20-year-old man was based on the integrity of the retinal functions, despite progressive worsening of muscular activity in the systems affected by the disease, and on the results of retinal fluorescein angiography. Although the changes in the pigment epithelium were not prominent ophthalmoscopically, they were clearly visible angiographically.

Atypical forms of retinal pigment dystrophy occurring during the course of ocular myopathy appear to be clinical expressions of a unique genetic defect confined to the pigment epithelial layer. We assume that the gene is capable of inducing a pleiotropic effect.

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THE EFFECTS OF LASER PHOTOCOAGULATION IN THE RETINAL CAPILLARIES

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Although pulsed ruby laser photocoagulation has been used widely in the treatment of several retinal diseases, the direct effect on the vessels is frequently questioned. Because of its high spatial coherence and selective absorption, as well as ease in obtaining continuous power, argon laser photocoagulation is recognized as a more useful tool in obliterating undesired vessels.[1,2] Despite the increase in interest in clinical application of these laser beams, only a few cytologic studies on the effects to the retinal vascular system after the treatment have been reported.[3-5]

We demonstrate the cytologic changes in the retinal capillaries and the retinal layers caused by both ruby and argon lasers, particularly the difference in effectiveness between the two lasers, and the effect of treatment of the intravitreal neovascularization.

MATERIAL AND METHODS

Laser lesions were produced on the normal retinas of 18 rhesus monkeys by using a ruby laser photocoagulator and an argon laser photocoagulator. Animals were anesthetized by intraperitoneal injections of sodium pentobarbital, and the heads were stabilized with a vacuum sandbag to determine the precise locations of treatment. Corneal transparency was maintained by frequent irrigation with physiologic saline solution.

Although various power levels of both lasers were used in the earlier experiments, we could not observe direct vascular damage in exposures of lower intensities. The power levels we used in this study are higher than that used in normal clinical doses. The intensity of the ruby laser was of clinical grade 3 with a field stop of 2.5 degrees according to the criteria of Noyori and associates.[6] Argon laser exposure was at the power level of 100 mW with the field stop of 500 μ and 500 msec duration. There were no appreciable differences by clinical criteria between the lesions produced by the two lasers. An average of 50 multiple lesions were placed in a 1-cm² area on the posterior pole and equatorial area of the eyes of each of 12 rhesus monkeys. Each lesion measured about 0.5 mm in diameter. The lesions were spaced at a distance twice the size of the lesion. Locations of certain lesions were carefully mapped in relation to clearly visible retinal blood vessels. These animals were examined frequently by ophthalmoscopy and fluorescein angiography. The retinas were studied immediately after treatment and on days 1, 3, 7, 14, and 30. One animal was killed seven months after treatment. The multiple ruby laser lesions were repeated three times on the same areas at one-month intervals in two monkeys. The animals were killed one month after the last exposure.

The animals were killed by overdose injections of pentobarbital. The whole eye with a small slit opening at the anterior portion was immersed in 4% glutaraldehyde in 0.15M phosphate buffer at room tempera-

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ture for a moment and then the eye was opened coronally. The exposed retinal areas were cut into wedges and we compared their gross appearances with those of fundus photographs and by fluorescein angiography. These pieces were washed with water and digested with 3% trypsin solution in 0.15M tris buffer at pH 7.8.[7] The isolated blood vessels were stained with PAS reaction and hematoxylin and were compared with the gross materials.

We selected small areas of the retina, including an exposed lesion randomly, and these were excised, postfixed in 1% osmium tetroxide in the phosphate buffer solution, dehydrated in ethyl alcohol and embedded in an epoxy resin. Sections 0.5 μ in thickness were stained with toluidine blue for general histologic study and ultrathin sections were examined electron microscopically after staining with uranyl acetate and lead citrate.

To simulate the condition of neovascularization in the vitreous cavity, a small amount of the whole blood of the same animal was withdrawn from an arm vein and was injected into the vitreous cavity near the posterior pole through the pars plana, using a 30-gauge needle. With the animal in a sitting position, the injected blood formed a thin film immediately anterior to the inner limiting membrane. In separate pilot experiments, the blood film measured about 80 to 100 μ thick at the lower portion of the coagula and 15 to 20 μ at the spreading upper margin. The injected blood films appeared to simulate the large intravitreal vessels at the lower portion and capillaries at the upper portion although these have no wall structure or stream movement. The retina was exposed to argon laser within one hour after the injection of the blood into the vitreous cavity. Argon laser exposures were performed after the clinical dosages for intraretinal treatment. Blood film at the aimed areas disappeared immediately after the laser exposure. Also, most of the blood film was lost during the sectioning procedure. Histologic and electron microscopic studies of the underlying retinas were performed similarly.

Results

Despite the difference in wavelength and absorption spectrum of the blood and pigment granules, ruby and argon laser exposures caused identical cell damage in the retina under these experimental conditions. The individual burn lesions, about 500 μ in diameter, were localized in the avascular outer layers of the retina. The pigment epithelium and the choroidal capillaries were also damaged severely. Since the damaged outer layers of the posterior retina are thick and removed from the vascularized inner layer, direct changes in the blood vessels in the thick posterior retina were small. However, we noted certain direct damage in the blood vessels in the peripheral retina, thinner than in the posterior pole. The cellular change in this area was more extensive.

Single exposure—Direct effect on the retina capillary—Flat preparations of the blood vessels immediately after exposure of either laser revealed a few dilated capillaries in the exposed area that contained more red blood cells. Also, a fine fibrous substance adhered to this capillary meshwork (Fig. 1) that lasted for about three days. No degeneration seemed to occur in the capillary at this stage. The capillaries in the adjacent unexposed area were intact.

By electron microscopy, we noted slight vacuolation, occasional swelling of mitochondria, and more pinocytotic vesicles in the endothelial cytoplasm (Figs. 2 and 3). Marginal infolds of the endothelial cells extended slightly. No noticeable change was present in the mural cells. We saw no coagulated serum or damaged blood cells within the blood vessels. The surrounding Müller's and neural cells were not affected. Both arteries and veins were not affected (Fig. 4) and the endothelial and muscle cells appeared to be completely normal. No sign of thrombosis was present in the lumen of large vessels.

DELAYED EFFECT ON THE CAPILLARY—The repair process of the damaged retinal tissue began immediately after the exposure. Degenerated debris of the photoreceptor cells was carried from the necrotic zone and the damaged pigment epithelial cells were replaced on the seventh day. Numerous macrophages were present in the subretinal space. The exposed areas were seen as white spots and regenerated pigment epithelial cells contained fewer melanin granules.

The capillaries that had been dilated in the earlier stage were normal within a few days. However, a small section of capillary in the exposed area contained endothelial cells with pyknotic and karyolytic nuclei (Fig. 5). These capillary walls were hyperchromatic and were sharply demarcated from the surrounding normal meshwork by the second week. These capillaries gradually evolved into acellular strands and remained in the retina for one to seven months. Angiography showed no abnormal hemodynamic disturbances, although the occluded fine capillaries were difficult to see because of the white background at the laser-exposed areas.

On the seventh day after the exposure, electron microscopy revealed that the photoreceptor cells had disappeared from the retinal tissue. The cytologic appearance of the inner layers was normal. Some blood capillaries in the exposed area showed pathologic changes. The cytoplasms of both endothelial and mural cells were shrunken and highly electron dense. Nuclei were pyknotic. The basement membranes were wavy and the capillary lumen contained debris substance. No blood cells were seen in the lumen.

After two weeks, the damaged capillaries became acellular strands consisting mainly of the basement membrane. We saw some cellular debris or cytoplasmic processes of Müller's cell in the lumen of the strand.

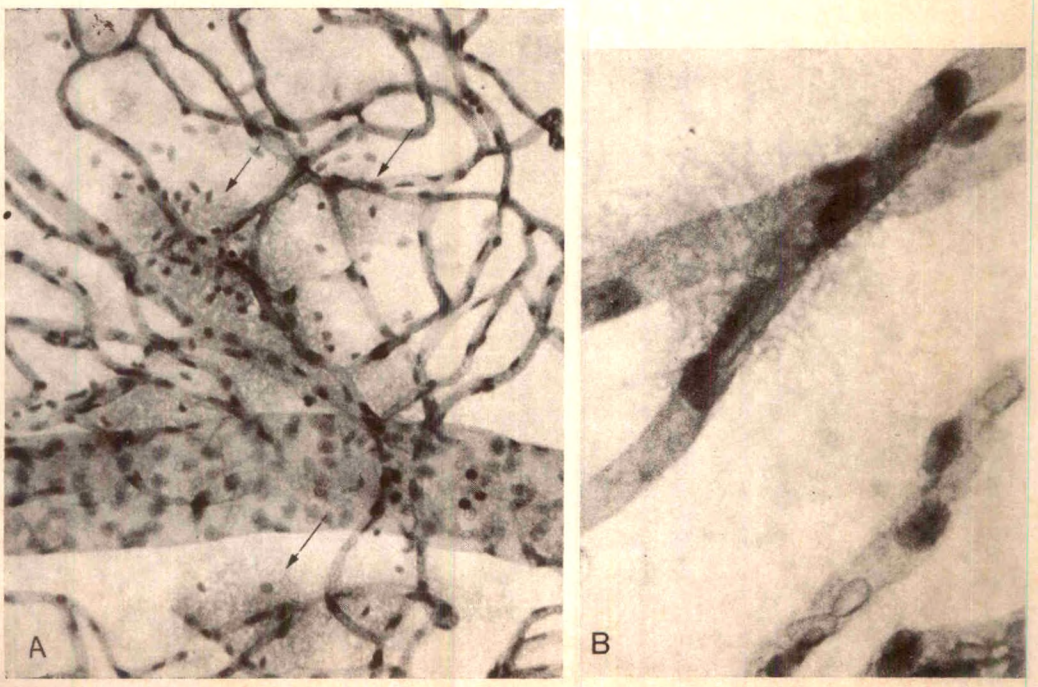


Fig. 1 (Okisaka, Kuwabara, and Aiello). Retinal blood vessels one hour after ruby laser treatment. A, Certain fibrous materials and a few neural cells are attached to the vessels in the treated foci indicated by arrows (×100). B, Higher magnification of capillaries. Vessels are dilated and contain more red blood cells, but cytologic appearance is normal (both in trypsin-digested flat preparation, PAS-hematoxylin staining, ×500).

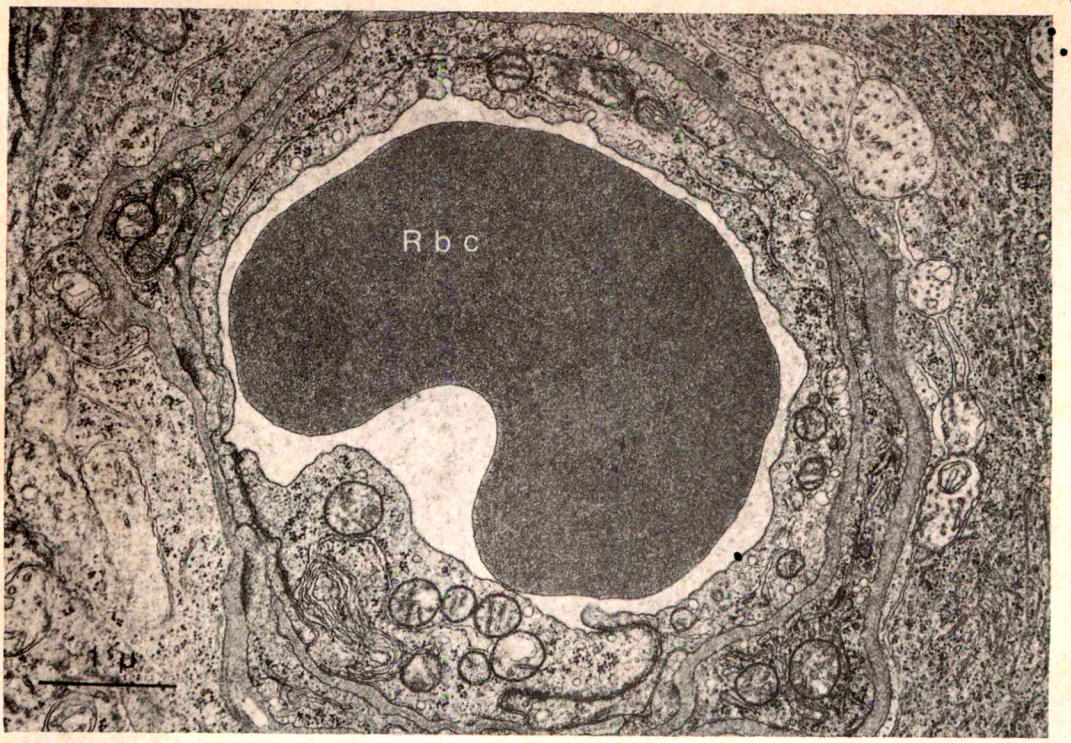


Fig. 2 (Okisaka, Kuwabara, and Aiello). Capillary in the nerve fiber layer of the retina of which outer layers have been damaged severely by argon laser 24 hours previously. The general appearance of the capillary is normal, but the endothelial cytoplasm contains a slightly increased amount of ribosomes and rough endoplasmic reticulum. Rbc indicates red blood cell (×18,000).

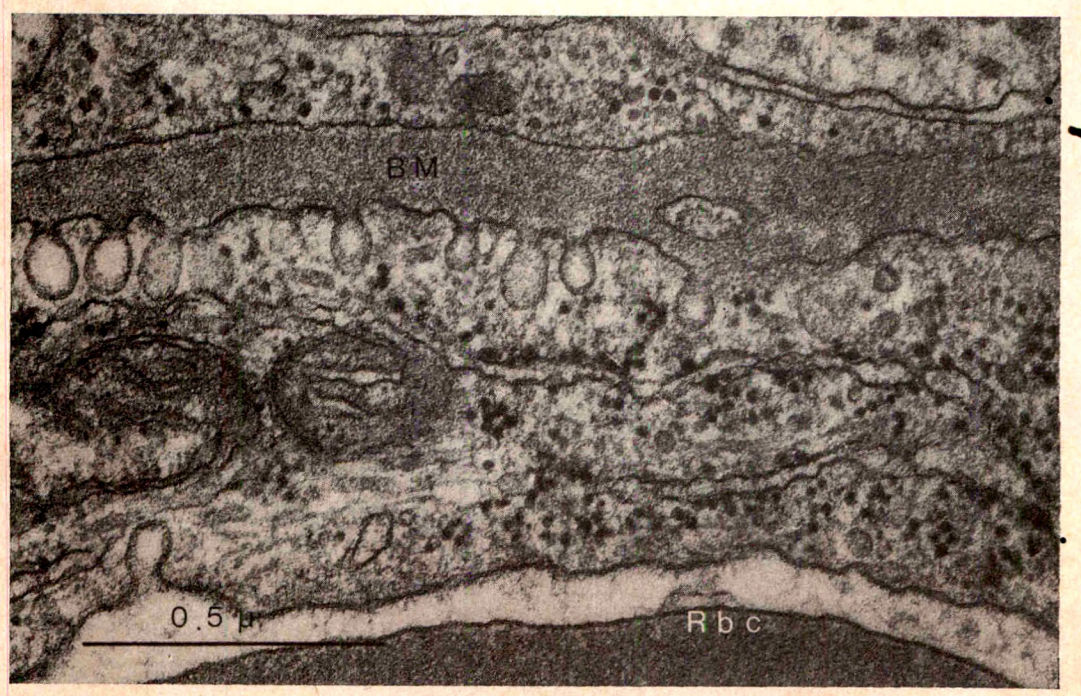




Fig. 4 (Okisaka, Kuwabara, and Aiello). Wall of a large artery was exposed to a grade 2 argon laser 24 hours before. Both muscle and endothelial cells appear to be normal. There may be more glycogen particles (dark arrow). The basement membrane (BM) seems to be normal (×18,000).

The surrounding cells, especially the adjacent ganglion cells, seemed to be normal. Although the retinas had multiple laser burns, the overall pattern of the flat preparation of the blood vessels in the treated area seemed to be the same as the normal vascular system. The acellular strands eventually shortened.

Repeated exposure—The retinas that received three series of multiple exposure, ending one month before, had mottled appearance formed by superimposed lesions with varying whitish appearances and pigmentation. The cytologic damage at these areas was extremely severe. The photoreceptor cells were extensively damaged but a few islands of tissue escaped the laser exposure. The number of nuclei of the photoreceptor and the bipolar cells was markedly diminished so that the retinal tissue was extremely thin. However, the innermost portion of the bipolar cell layer and the ganglion cells appeared to be well preserved. Spots consisting of only thin membranous glial cells were present, intermingled with lesions of varying sizes. The pigment epithelium adhered to the retinal glial tissue. Moreover, Bruch's membrane adhered to the retina directly in areas from which the pigment epithelium had disappeared.

Although large vessels were patent, capillaries showed considerable changes. There were many segments of acellular strands in the vasculature (Fig. 6). The degree of damage to the vessels corresponded to the severity of cellular destruction. Normal cap-

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Fig. 3 (Okisaka, Kuwabara, and Aiello). Higher magnification of a part of the capillary wall. Pinocytotic vesicles are abundantly attached to the basement membrane (BM). Rough endoplasmic reticulum is abundant in this area; Rbc indicates red blood cell (×80,000).

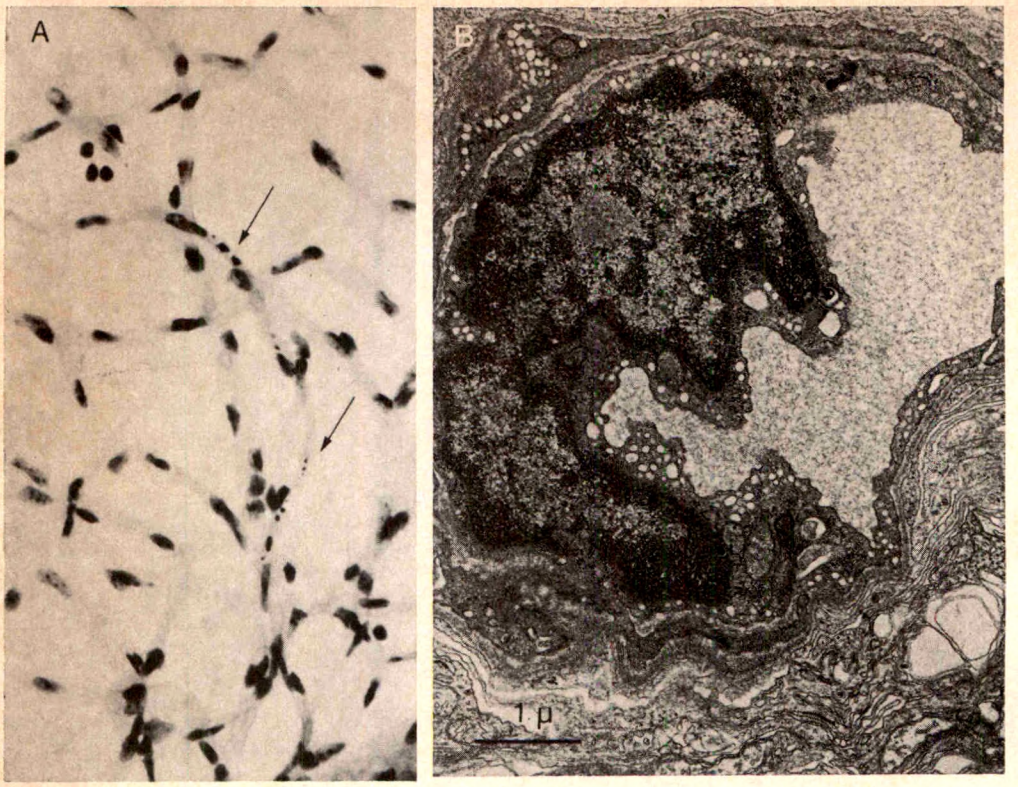


Fig. 5 (Okisaka, Kuwabara, and Aiello). Retinal vessels one week after ruby laser exposure. A, A few pyknotic and karyolytic nuclei of the endothelial cells (arrows) are present in a short segment of the capillary mesh within the exposed area (×180). B, Electron micrograph of a capillary in a similar area. Cytoplasms of both endothelial and mural cells are vacuolated. The cytoplasms and the nucleus are slightly electron dense (×14,000).

illaries intermingled with acellular strands but the normal vascular pattern was maintained. Because of the large white background, we did not obtain the details of the capillary pattern by fluorescein angiography. The vascular pattern of the adjacent untreated area was normal.

By electron microscopy, blood vessels in the one-month-old lesions after repeated burns were either obliterated strands or normally patent capillaries. The damaged capillary consisted of irregularly collapsed basement membranes and occasionally surviving mural cell cytoplasm. The surrounding neural tissue was also damaged. The cytoplasm of Müller's cell contained more glycogen and electron-dense particles, presumably melanin granules (Fig. 7). The normal vessels showed relatively thick endothelial linings and thickened basement membrane.

Choroidal capillaries were present beneath the surviving pigment epithelium. However, in the area from which the pigment epithelium had disappeared, choroidal vessels were absent.

Effects of argon laser photocoagulation on the blood in the vitreous surface of the retina—THICK BLOOD FILM—The argon laser exposure on the blood film in the vitreous cavity produced whitish retinal lesions of varying sizes depending on the thickness of the blood film. The appearance of the retinal lesions was similar to that in the clinical treatment of large blood vessels in the vitreous cavity. Blood cells of the exposed area disappeared instantly on exposure and the underlying retinal tissue became whitish.

The exposure that was aimed at the thick blood film in the vitreous cavity caused severe degeneration in the nerve fiber and the ganglion cell layers (Fig. 8, short arrow). The ganglion cells were vacuolated and their nuclei were pyknotic. The nerve fibers had disintegrated. All other retinal layers, the pigment epithelium, and the choroidal capillaries were also damaged considerably. The degenerated debris were present in the area for about one week and were then absorbed gradually. One month later, the damaged inner layer of the retina was an extremely thin tissue consisting mainly of Müller's cells (Figs. 9 top, and 10). The other layers of the retina were also thin and the capillary bed was absent in this area. Photoreceptor cells were disorganized. The pigment epithelial cells had regenerated but their sizes and pigmentations were irregular.

THIN BLOOD FILM—An argon laser



Fig. 6 (Okisaka, Kuwabara, and Aiello). Retinal vessels one month after three sessions of argon laser treatment. Many capillaries are acellular strands. However, despite severe damage in the photoreceptor layer, many capillaries are patent (trypsin-digested flat preparation, PAS-hematoxylin staining, ×60).

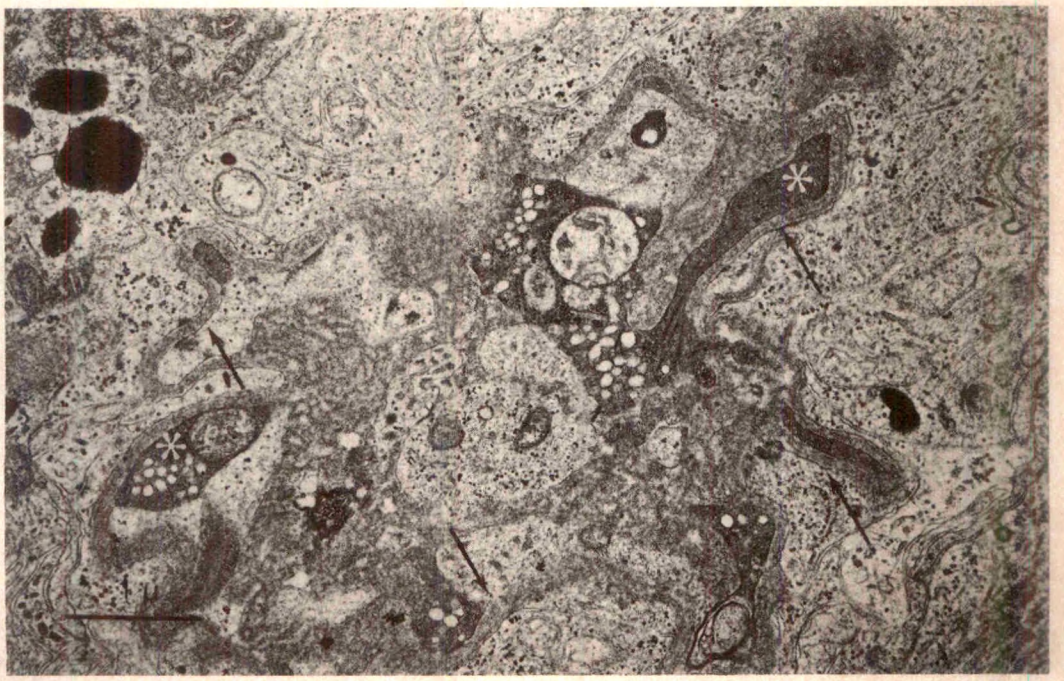


Fig. 7 (Okisaka, Kuwabara, and Aiello). Cross section of an acellular strand in the inner layer of the retina that was damaged severely by three sessions of argon laser exposure one month before. The strand consists of collapsed and wavy basement membrane (arrows) and surviving portions of electron-dense mural cells (asterisks). The endothelial cell and the lumen are absent. The surrounding retinal tissue contains abundant glycogen granules (×18,000).

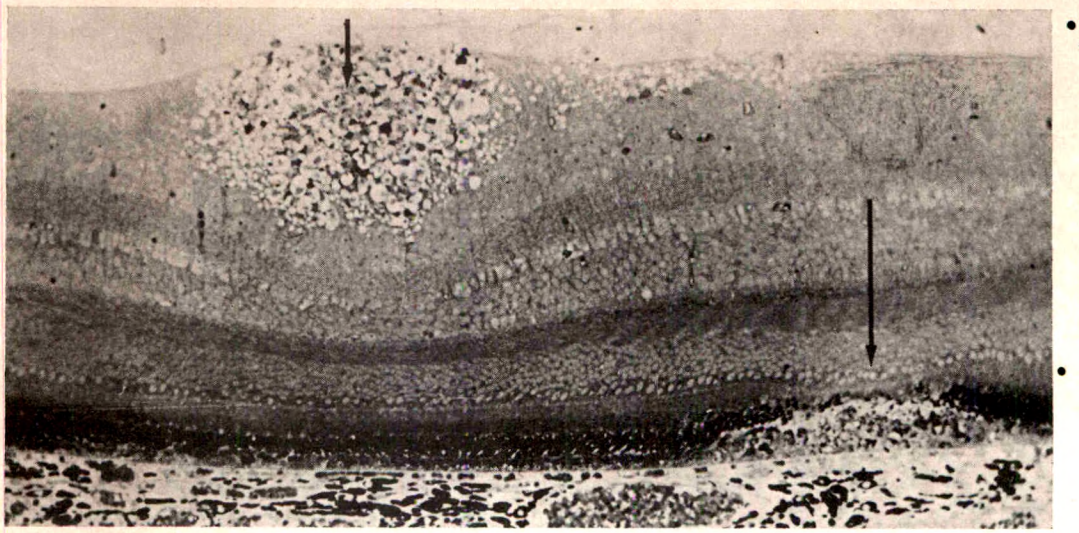


Fig. 8 (Okisaka, Kuwabara, and Aiello). Blood film over the retinal inner surface was exposed to argon laser one hour before. The blood was washed away during the histologic processing but the thickness of the blood film is about 80 μ (short arrow) and about 10 μ (long arrow). There is severe damage in the ganglion cell and nerve fiber layers (short arrow), whereas the damage is localized in the photoreceptor and the pigment epithelial layers (long arrow) (epoxy section, toluidine blue staining, ×100).

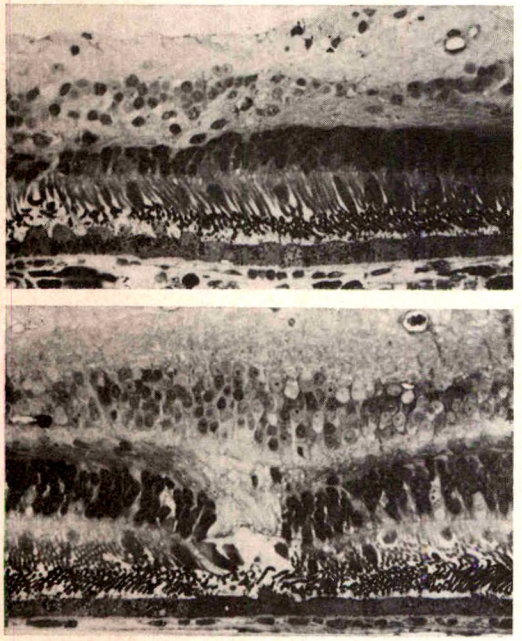


Fig. 9 (Okisaka, Kuwabara, and Aiello). Retinal tissue damaged six months before by argon laser exposure similar to Figure 8. Top, Damaged inner layer lost ganglion cells and is a thin glial tissue. The photoreceptor cell layer is damaged moderately. Bottom, Damaged photoreceptor layer left a small tissue defect. The inner layers appear to be normal (both epoxy sections, toluidine blue staining, ×180).

beam aimed at the 15- to 20-μ thick blood film simulating vitreous neovascularization burned out the blood streaks effectively and caused white burn spots in the underlying retina. The cytologic appearance of the retinal damage was identical to that of usual laser treatment of the retina (Figs. 8, long arrow, and 9, bottom). The photoreceptor cells and the pigment epithelium were severely damaged. The white burn spots were formed by a process similar to that used in regular laser treatment. Blood vessels in the inner layer of the retina were not damaged directly by the beam, but the delayed changes are similar to those observed above.

The thicker the blood film, the more advanced were the cellular damages in the inner layers of the retina including the ganglion cells. Consequently, we noted varied changes in the cellular elements and in the vascular system.

Discussion

When the normal monkey retinas were exposed to beam energy similar to that used in the clinical treatment of vascular diseases,

the pattern and nature of the cellular destruction by both lasers were identical. When the lasers were aimed at the blood vessels in the retina, the heat energy of both lasers was absorbed by the pigment epithelium and severe damage was caused in the nonvascular photoreceptor layer. Direct damage to the blood vessels was small. Only small segments of blood vessels situated in the path of the beam showed a slight reaction in the endothelium, but no immediate occlusion was demonstrated in this area. Red blood cells that received heat energy, particularly by argon laser, may have been damaged, but were carried rapidly away from the area by the blood stream.

A few capillaries in the exposed area showed delayed reaction. Short segments of capillaries in the burned lesion showed degeneration when the repairing process of the retinal cells progressed considerably. Two to three weeks after the treatment, damaged photoreceptor cells and the pigment epithelium in individual lesions were replaced by adjacent intact cells, apparently by a sliding phenomenon. The retinal tissue in the treated area contained numerous small spots from which many photoreceptor cells disappeared. Only a few segments of the capillaries within these foci became nonfunctioning strands. This delayed change of the capillary may suggest a decrease of the vascular requirement due to the reduction of metabolically active cell elements from the retina because of the laser burns. The retinal tissue may be eliminating unnecessary capillaries from the burned area as a type of economizing response of the tissue. In certain pathologic conditions of the photoreceptor elements of the retina, we commonly found clinicopathologically obliterated capillaries in the retina. The pathologic



Fig. 10 (Okisaka, Kuwabara and Aiello). A portion of the gliosed inner layer of the retina (Figure 9, top) consists of fine processes of Müller's cell and a few glial cells. Remnants of blood vessels are seen as pieces of basement membrane (dark arrows) (×13,000).

changes of the vascular system in the retinas of retinitis pigmentosa may be due to a similar etiology. Similar vascular changes have been demonstrated experimentally in light-damaged rat retinas.[8]

Since laser treatment of diabetic retinopathy in the human is the same as in monkeys, similar vascular effects may occur in the abnormal human retinas. Although the main purpose of the treatment is to obliterate undesirable blood vessels, immediate occlusion of the blood vessels may not be expected. Perhaps the underlying photoreceptor cells, usually well preserved in the diabetic retina, are severely damaged as shown in this experiment. Obliteration of a few segments of capillaries at each damaged region including pathologically altered vessels such as dilated and microaneurysmic ones may be occurring similarly. Elimination of these leaky blood vessels controls diabetic retinopathy. The preventive effect of further retinopathic changes after extensive laser treatment has been reported.[9] The massive placement of laser burns in the posterior retina results in a marked reduction of functional retinal cells and some blood vessels. The whole process may be analogous to the surgical excision of the tissue; there will be less retinal tissue to produce retinopathy.[10] However, there is relatively small visual dysfunction in patients who receive extensive laser treatment.[9] The retinal tissue may have excessive photoreceptor cells and only a portion of those cells may be necessary for the maintenance of the function. Horizontal connections of neural cells with the horizontal cells and with amacrine cells have been demonstrated clearly in recent studies.[11] The visual function in retinas with multiple localized destruction of the photoreceptor cells appears to be compensated by these neural cells.

One of the most important applications of laser treatment in diabetic retinopathy is the elimination of the vascularized vitreous tissue. Argon laser has been used widely for this purpose.[12] The exposure of argon laser on the thick blood film that simulates a large vessel in the vitreous cavity causes severe cellular damage in the inner layers of the retina including the ganglion cells. Many red blood cells are eliminated instantly from the vitreous cavity by the exposure, and whitish spots form in the underlying retina. Although the cooling effect of the blood stream was absent in this study, the appearance of the lesion is identical to that of clinically treated retinas. If the vitreous vessels are large, the retinal damage includes the ganglion cells. Since the ganglion cells are believed to be essential in maintaining visual conduction, severe visual impairment may result from laser damage of this nature. The laser beam appears to eliminate satisfactorily small vitreous vessels while some burn damage in the outer retinal layers is observed. The cellular damage of the photoreceptor cells may be beneficial in preventing angiopathy. However, extensive treatment by argon laser especially with the "painting" technique may damage ganglion cells and their nerve fibers.

Summary

Using ruby and argon lasers, we produced multiple lesions on normal rhesus monkey retinas. The clinically used energy levels of both lasers produced identical cellular changes in the retina. Neither laser directly produced obliteration of capillaries. However, after the cellular damage in each burn lesion was repaired, we observed delayed degeneration of capillaries in a small segment at the burned areas. The marked reduction of active retinal cells that reduce vascular activity may beneficially affect laser treatment of diabetic retinopathy. The retinal tissue appears to have excessive photoreceptor cells and the horizontal connection of other cells seems to compensate for visual function after loss of many photoreceptor cells. We demonstrated severe damage in the ganglion cells by argon laser when it was aimed at the thick blood films in the vitreous cavity. Certain precautions must be

taken when peripapillary neovascularization is treated by laser beam.

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Ophthalmic miniature

It is fascinating that the word "explore" does not apply to the searching aspect of the activity, but has its origins in the sounds we make while engaged in it. We like to think of exploring in science as a lonely, meditative business, and so it is in the first stages, but always, sooner or later, before the enterprise reaches completion, as we explore, we call to each other, communicate, publish, send letters to the editor, present papers, cry out on finding.

Lewis Thomas, *The Lives of a Cell. Notes of a Biology Watcher*
Viking Press, 1974

GLIAL CELL PROLIFERATION IN RETINAL DETACHMENT (MASSIVE PERIRETINAL PROLIFERATION)

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In human retinal detachment cellular membranes can be found lying on the inner or outer surfaces of the retina and on vitreous structures. These membranes have been examined light microscopically by many authors but the origin of the cells has not been completely determined.[1,2] Since similar membrane formations have been observed in experimental retinal detachments in owl monkeys, we have studied these membranes in order to clarify the origin of the cells involved. In a previous study we presented evidence that some of the proliferating cells are derived from the pigment epithelium.[3] In this paper the preretinal and subretinal proliferation of glial cells will be described.

MATERIALS AND METHODS

Retinal detachments were produced in owl monkey eyes by a method previously described.[4] One hour to 27 months after production of the retinal detachment, the eyes were enucleated and prepared for light and electron microscopy and autoradiography (Table).

For light microscopic evaluation the whole eye was fixed in a modified Kolmer fixative.[5] To preserve the shape of the eye, 0.1 ml of fixative was injected into the anterior chamber. After 24 hours of fixation the cornea was removed with a trephine to avoid deformation of the globe during dehydration and to allow embedding material better access to intraocular structures. The globes were embedded in paraffin after dehydration. Vertical sections, 5 μ in thickness, were made in five areas: through the retinal hole (located temporally); through the macular area; through the disk; and through nasal parts of the eye at distances from the disk corresponding to those of the first two areas. All histological sections were stained with hematoxylin-eosin and PAS.

For electron microscopic evaluation 0.2 ml of fixative was injected through the pars plana into the vitreous cavity immediately before enucleation. The whole eye was then enucleated and immersed in 6% phosphate-buffered glutaraldehyde. The eye was opened circumferentially anterior to the ora serrata. Areas of interest were photographed while immersed in fixative, then excised and post-fixed in 2% phosphate-buffered osmium tetroxide, dehydrated in a graded series of alcohol, and embedded in Epon. Sections 1.5 μ thick for light microscopic evaluation were stained with paraphenylenediamine. Thin sections (0.05 μ) were stained with uranyl acetate and lead citrate and examined with a JEM-7 electron microscope.

For autoradiographic studies 0.1 ml tritiated thymidine (50 μCi thymidine methyl-H-3, specific activity 5.0 curies/mm) was injected intravitreally two hours before enucleation. Sections were coated with Kodak nuclear track emulsion NTB2, exposed for five to 14 days, and developed in Kodak D19. Paraffin-embedded sections were stained with hematoxylin-eosin; Epon-embedded sections remained unstained.

From the Bascom Palmer Eye Institute, University of Miami School of Medicine, and the Veterans Administration Hospital, Miami, Florida.

This study was supported in part by Public Health Service Research grant EY-00841; in part by the Veterans Administration Hospital, Miami; in part by the Florida Lions Eye Bank, Inc., Miami, Florida. Doctor Laqua is supported by a Research Fellowship (La 305/1) from Deutsche Forschungsgemeinschaft, Bonn, Germany.

Presented in part at the Association for Research in Vision and Ophthalmology Spring Meeting, Sarasota, Florida, April 25-29, 1974; and the Ninth Meeting of the Club Jules Gonin, LaBaule, France, May 12-18, 1974.

Reprint requests to Robert Machemer, M.D., P.O. Box 520875, Biscayne Annex, Miami, FL 33152.

Results

Preretinal proliferation of glial cells—As early as four weeks after production of the retinal detachment preretinal tissue can be found which typically is connected to the underlying retina by a small bridge of tissue. The extent of the proliferation and its effect on the underlying retina varied considerably in different specimens.

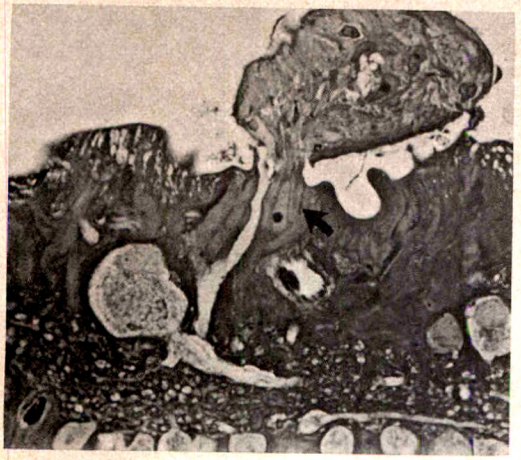
In some cases a small clump of tissue consisting of irregularly arranged cells was visible on the inner retinal surface. These cells had abundant cytoplasm. Only a few nuclei with occasionally prominent nucleoli were found. The preretinal tissue was connected to the underlying retina by a small bridge in which a retinal cell, apparently migrating out of the retina, was identified. In the underlying retina there was wrinkling of the internal limiting membrane and the nerve fiber layer (Fig. 1,A).

The preretinal tissue may have been more extensive and formed a small membrane in which the cells tended to have a parallel arrangement. They contained abundant cytoplasm and oval to spindle-shaped nuclei. The tissue was connected to the retina by a thin bridge through which a retinal cell apparently migrated out of the retina. In the retina itself cells were seen that greatly resembled the outgrowing cell. These cells had large oval to spindle-shaped nuclei with prominent nucleoli. Definite wrinkling of the internal limiting membrane and the nerve fiber layer occurred in the retina underlying the preretinal tissue (Fig. 1,B).

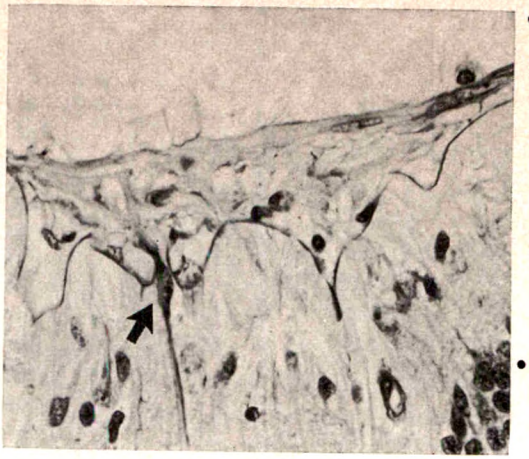
TABLE

SURVEY OF EXAMINED EYES

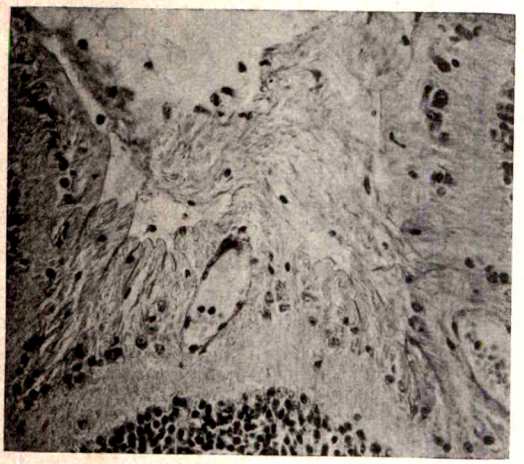
Duration of Retinal Detachment	No. of Eyes	Eyes Used for Autoradiography	Eyes with Glial Proliferation Proven by	
			Light Microscopy	Electron Microscopy
Hr 1	6			
6	2			
12	2			
18	2			
Day 1	13	6		
3	6	4		
Wk 1	9	6		
2	6	2		
3	2			
4	26	14	6	3
5	6	3	3	
6	1			
8	6	3	2	
9	17	16		6
10	7	4	4	1
12	6		3	
14	2			
16	2	2		
17	2	2	2	
18	1		1	
Mo 5	2		2	
6	1			
8	2			2
11	2		1	1
27	1	1	1	
Total	132	63	25	13



A



B



C

Fig. 1 (Laqua and Machemer). A, Small clump of preretinal glial cells connected to the retina by a thin bridge of tissue. A retinal cell is migrating out of the retina (arrow). There is wrinkling of the internal limiting membrane and the nerve fiber layer in the underlying retina (paraphenylenediamine, phase contrast, ×400). B, Small preretinal glial membrane connected to the retina by a thin bridge of tissue. A retinal cell is migrating out of the retina (arrow). In the retina itself, cells are seen closely resembling the cell about to migrate through the internal limiting membrane (PAS, ×400). C, Extensive preretinal glial proliferation causing not only wrinkling of the internal limiting membrane but also full-thickness folding of the retina. Connections between the preretinal tissue and the retina are frequently found close to vessels (PAS, ×160).

More extensive preretinal tissue may cause even more folding of the retina. Not only the internal limiting membrane but the entire retina may fold. The preretinal tissue appeared fibrillar and connections to the underlying retina were seen on close examination of serial sections. These connections were frequently found close to blood vessels (Fig. 1,C).

Electron microscopically, the preretinal tissue contained cells with oval to spindle-shaped nuclei sometimes irregularly indented. The cytoplasm was packed with parallelly arranged filaments aligned along the axis of the cell process. The cytoplasm had only a few other organelles, such as some microtubules, perinuclear rough endoplasmatic reticulum, and glycogen granules. Many cells had basement membranes and were connected to each other by desmosomes or zonulae adherens (Fig. 2). On the surface of the preretinal tissue the cells developed a basement membrane, or microvilli and zonulae adherens, or no specific structure at all (Fig. 3). Because of all the above morphologic features, we identified these cells as astrocytes.

In these astrocytes, the amount of cytoplasmic filaments may vary. Cell processes with a large amount of cytoplasmic filaments were found belonging to cells more precisely classified as mature, fibrous astrocytes. However, there were also cell processes contain-

ing fewer filaments and therefore classified as belonging to younger, less differentiated astrocytes (Fig. 4).

Electron microscopic examination of the bridge of tissue connecting the retina to the preretinal glial tissue shows a definite break in the internal limiting membrane with rolled over edges. Cell processes had grown out through the break but some remained partly attached to the internal limiting membrane. They were connected to each other and to adjacent intraretinal Müller cell processes by desmosomes. The processes contained smooth endoplasmic reticulum, abundant cytoplasmic filaments, and glycogen granules. At the edge of the break in the internal limiting membrane an excessive formation of basement membrane may be present. The cell

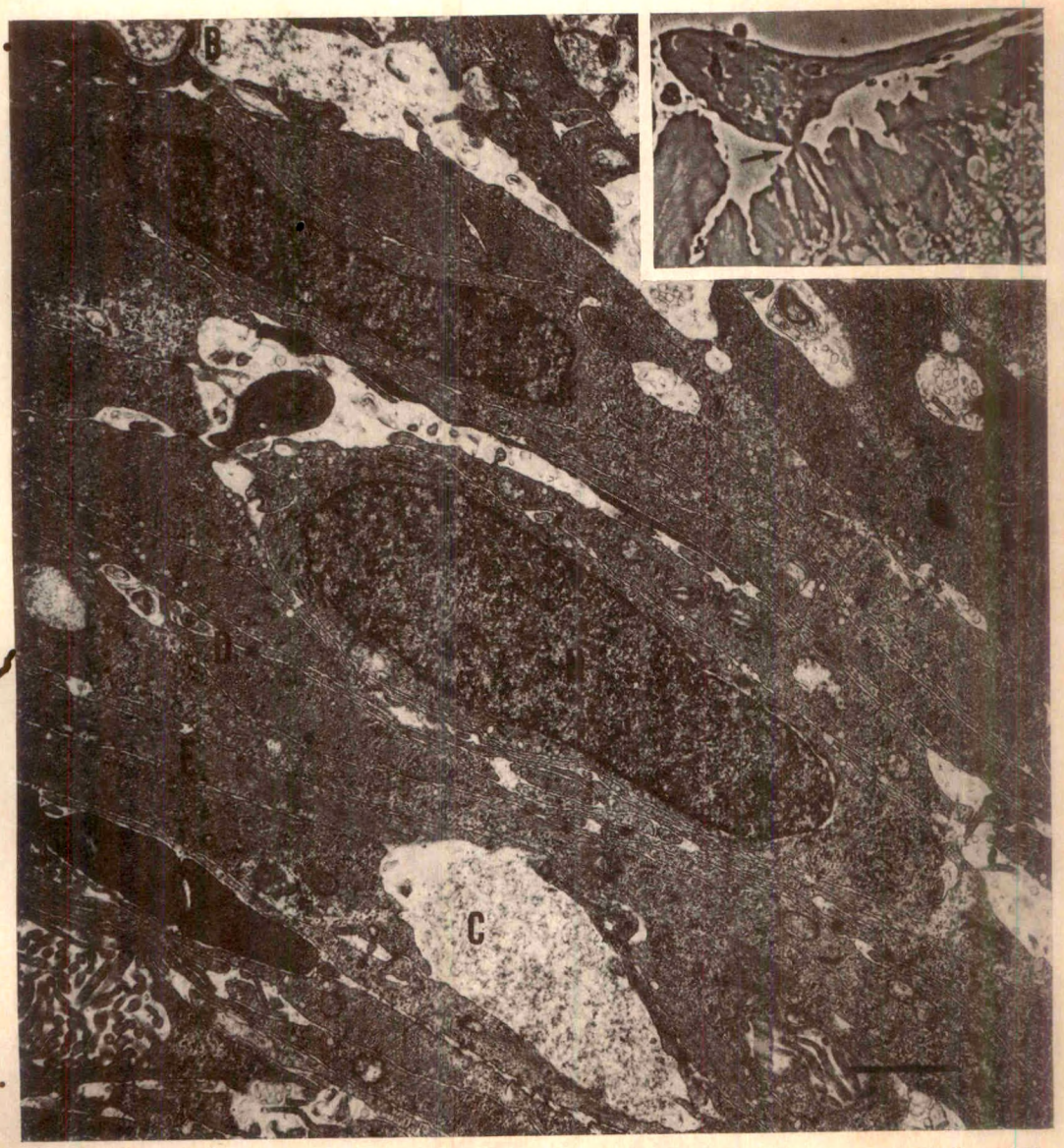


Fig. 2 (Laqua and Machemer). Preretinal membrane consisting of fibrous astrocytes. Nucleus (N); cytoplasmic filaments (F); desmosome (D); basement membrane (B); collagenous material between fibrous astrocytes (C). Inset, Light microscopy of the same preretinal membrane. Break in the internal limiting membrane (arrow) is shown in Figure 5 (paraphenylenediamine, ×250). Bar gauge = 1 μ.

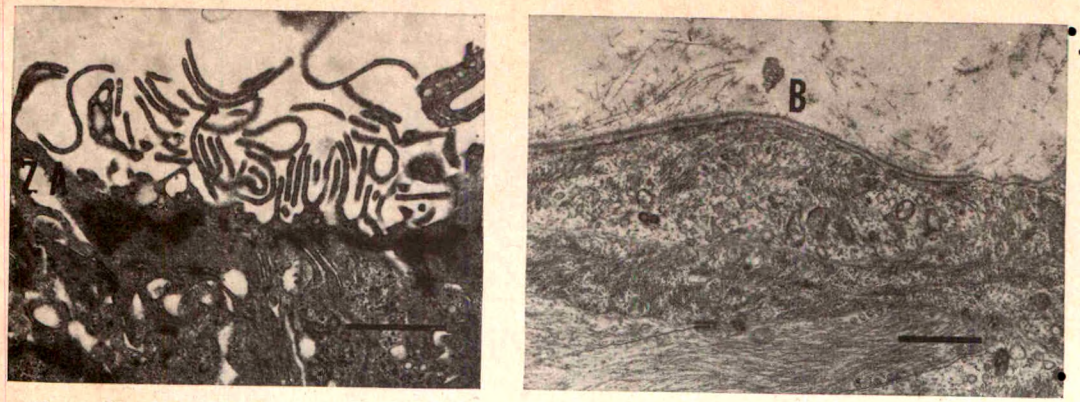


Fig. 3 (Laqua and Machemer). On the surface of the glial membranes, the cells may develop a basement membrane (B) or microvilli and zonulae adherens (ZA). Bar gauge = 1μ.

processes occasionally may be continued to the inner nuclear layer. Because of these features, we interpreted the cell processes as belonging to Müller cells (Fig. 5). However, inner Müller cell processes participated in the formation of the preretinal glial tissue only in the immediate area of the break.

Autoradiographs after tritiated thymidine injection showed labeling of cell nuclei in the preretinal glial tissue. This indicated DNA synthesis and showed that the cells were actually proliferating and not simply migrating out of the retina (Fig. 6).

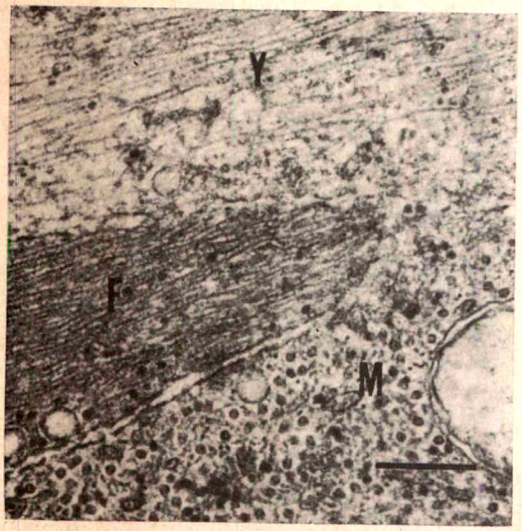


Fig. 4 (Laqua and Machemer). In preretinal as well as in subretinal glial membranes cell processes with varying amounts of filaments are found. Cells containing fewer filaments but often more microtubules (M) are interpreted as younger, undifferentiated astrocytes (Y). Cells with a large amount of cytoplasmic filaments are interpreted as mature, fibrous astrocytes (F). Bar gauge = 0.2 μ.

Subretinal proliferation of glial cells—As early as four weeks after production of a retinal detachment subretinal tissue could be found which typically had multiple localized connections to the outer retina. The extent of the proliferation and its effect on the retina varied in different specimens.

A small clump of subretinal cells connected to the retina by bridges of tissue was seen. This clump consisted of irregularly arranged cells with abundant fibrillar cytoplasm and oval to spindle-shaped nuclei. The same type of cell was found in the connecting bridge and also in the outer retina. These cells seemed to have displaced cells in all retinal layers from the external limiting membrane to the inner nuclear layer. Moreover, all these retinal layers appeared to be pulled outward toward the subretinal proliferation (Fig. 7,A).

The subretinal tissue may be more extensive and may form a small membrane. Typically, subretinal membranes consisted of multiple layers of parallelly arranged, densely packed cells. These cells had abundant, fibrillar cytoplasm and spindle-shaped nuclei. The membrane may have several attachments to the outer retina. At these attachment points no external limiting mem-

brane was found and a firm connection between the subretinal tissue and the retina existed. The entire retina from the external limiting membrane to the inner nuclear layer appeared to be pulled outward. The effect of even small membranes on the retina was extensive and may have caused a full-thickness fold (Fig. 7,B).

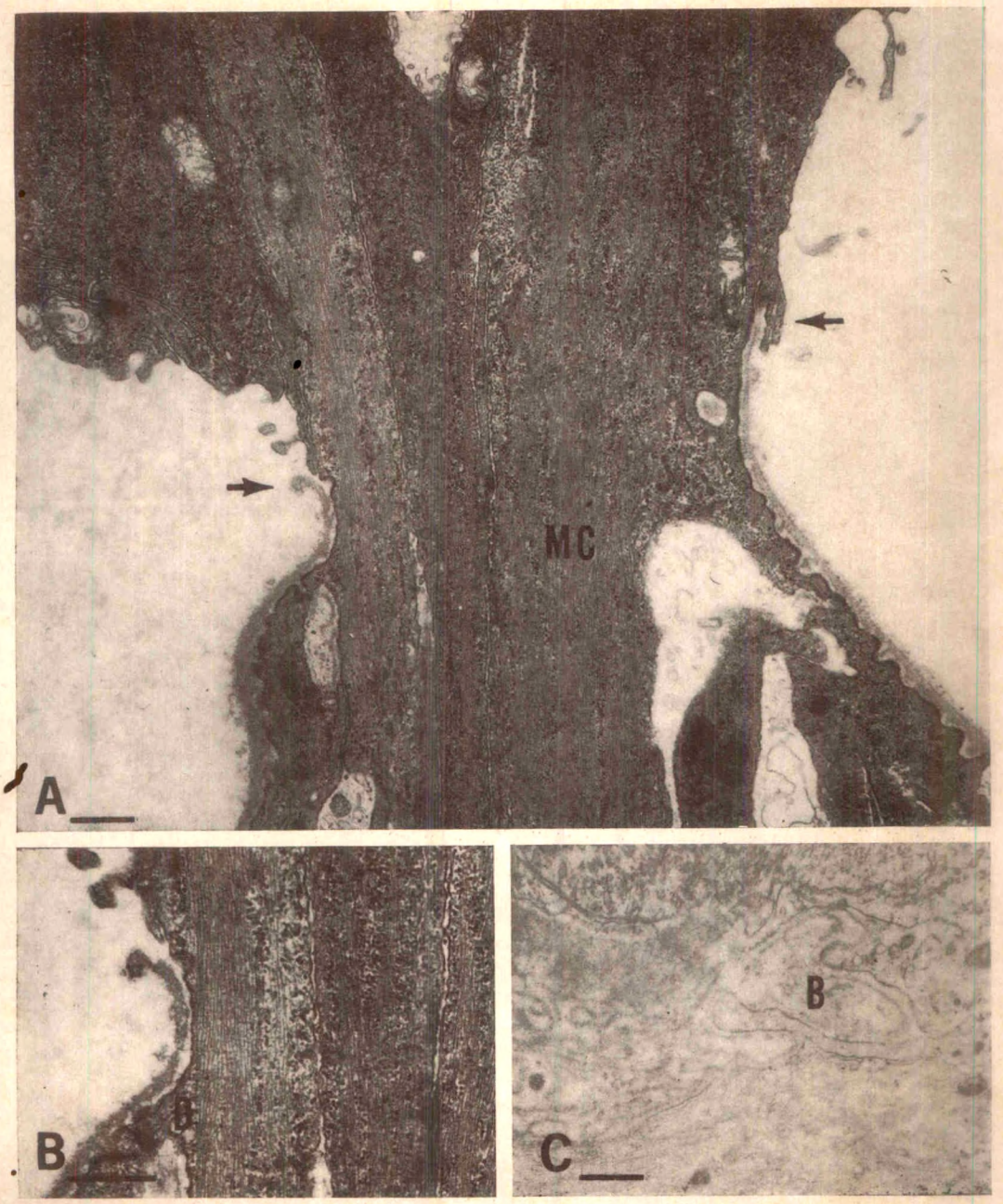
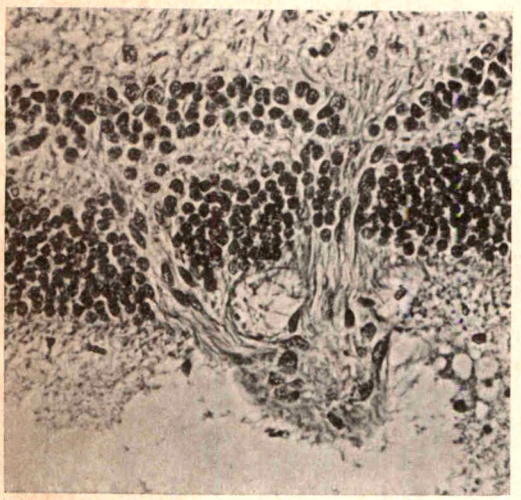


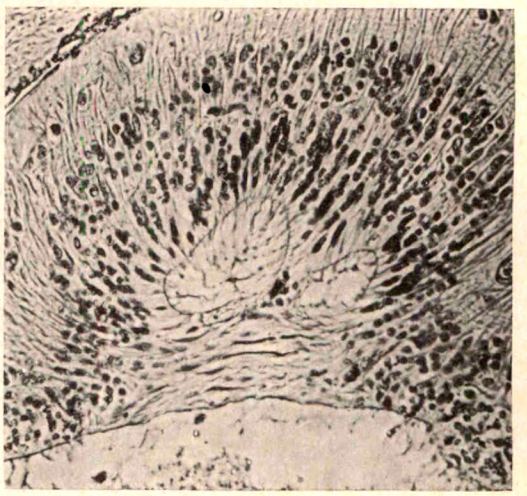
Fig. 5 (Laqua and Machemer). A, Break in the internal limiting membrane (arrows) and outgrowing Müller cell processes (MC) which remain partly attached to the internal limiting membrane (same specimen as Figure 2, inset). Bar gauge = 0.5 μ. B, Outgrowing Müller cell processes are connected to each other and to adjacent intraretinal Müller cells by desmosomes (D). Bar gauge = 0.5 μ. C, At the edge of the break, excessive basement membrane (B) formation may be found. Bar gauge = 0.5 μ.



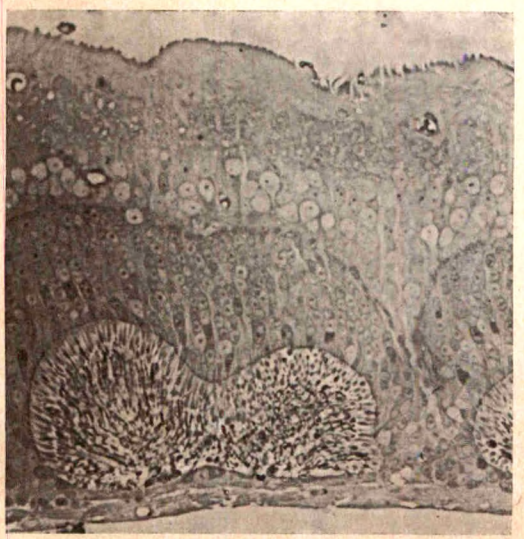
Fig. 6 (Laqua and Machemer). Radioactive labeling of cell nuclei (arrow) in a small tuft of preretinal glial tissue indicates DNA synthesis and shows that the cells are actually proliferating and are not only migrating out of the retina (×400).



A



B



C

Fig. 7 (Laqua and Machemer). A, Clump of subretinal glial cells connected to the retina by thin bridges of tissue. Glial cells displace cells in the various layers from the external limiting membrane to the inner nuclear layer (PAS, phase contrast, ×250). B, A small subretinal glial membrane is attached in three areas to the outer retina. At these attachment points the outer retina appears to be pulled outward toward the subretinal membrane (PAS, phase contrast, ×250). C, A large subretinal glial membrane with attachment points to the outer retina. The photoreceptor layer is pulled into the membrane. The retina is markedly folded (paraphenylenediamine, phase contrast, ×160).



Fig. 8 (Laqua and Machemer). Subretinal membrane consisting of fibrous astrocytes. Nucleus (N); cytoplasmic filaments (F); basement membrane (B); zonulae adherens (ZA); extracellular collagenous material (C). Inset, Light microscopy of the same subretinal membrane. Note fibrillar material (F) between the outer retina and the subretinal membrane (see Figure 14) (PAS, ×160). Bar gauge = 1 μ.

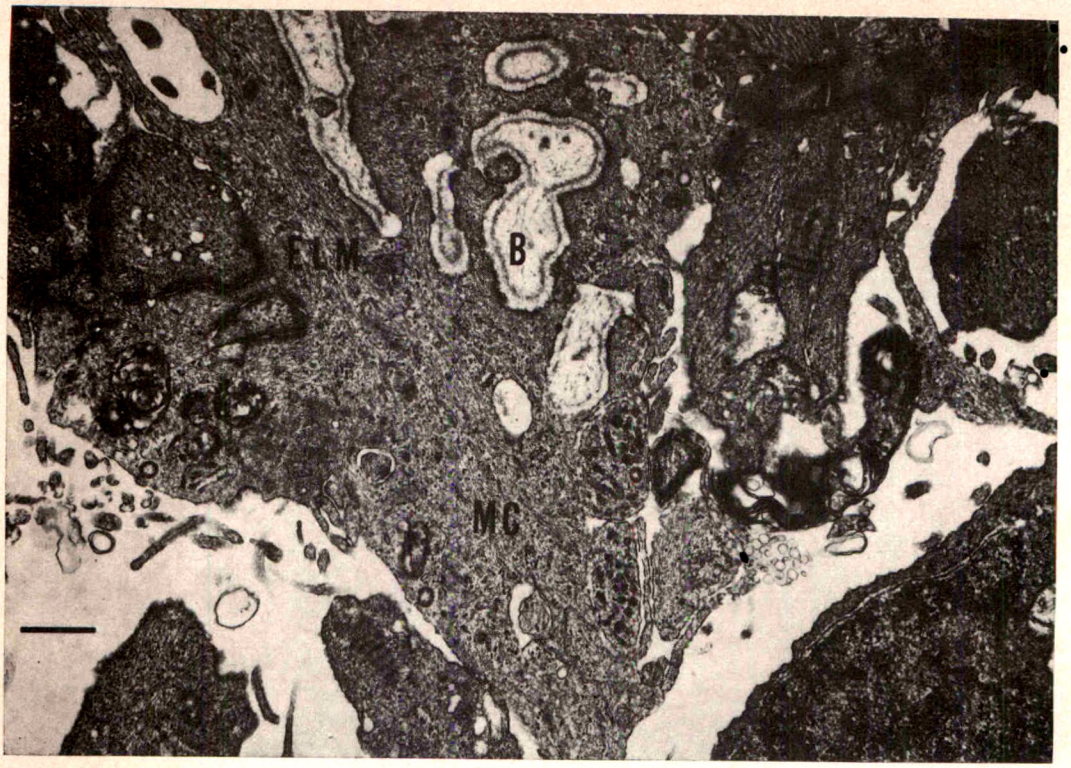


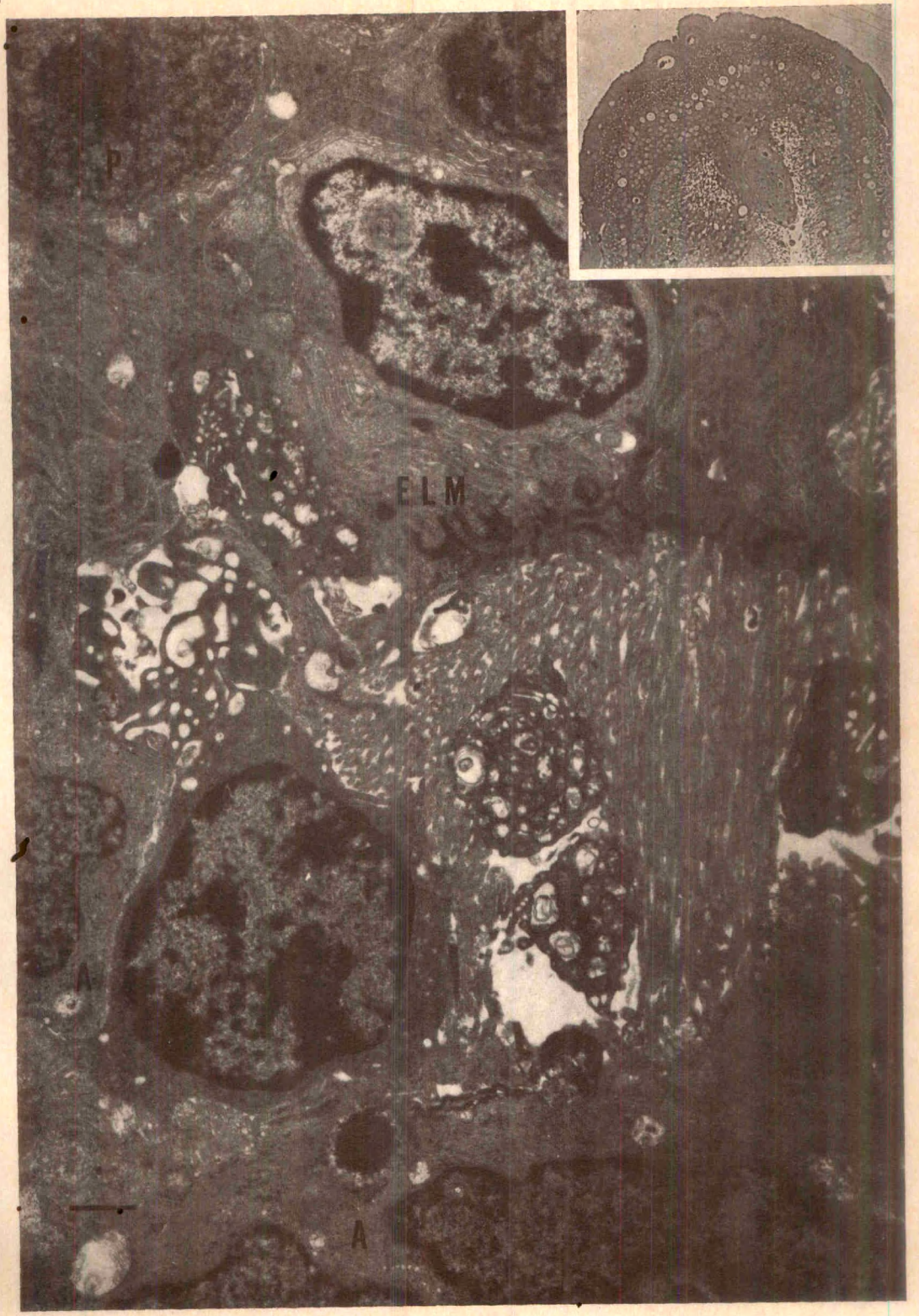
Fig. 9 (Laqua and Machemer). Focal interruption of the external limiting membrane with outgrowing Müller cell processes (MC) which participate in the formation of the external limiting membrane (ELM). Basement membrane (B) and extracellular filamentous material adjacent to Müller cell process. Bar gauge = 0.5 μ.

Larger membranes covered the outer surface of the retina and had multiple attachment points to the retina. Here the photoreceptor layer was pulled into the subretinal membrane and photoreceptor nuclei were found in the membrane. The retina was extensively folded and had a scalloped appearance (Fig. 7,C).

Electron microscopically, the subretinal tissue consisted of cells with nuclei that were typically oval to spindle shaped. The cytoplasm was filled with parallelly arranged filaments aligned along the axis of the cell process. In addition, perinuclear rough endoplasmatic reticulum, some glycogen granules, and microtubules were seen. The cells were often lined by a basement membrane and connected to each other by desmosomes or zonulae adherens (Fig. 8). The surface of the subretinal membrane was lined by a basement membrane, developed microvilli and zonulae adherens, or had no specific structure. Because of the foregoing morphologic features, we identified these cells as astrocytes. Cell processes with a large amount of cytoplasmic filaments are believed to belong

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Fig. 10 (Laqua and Machemer). Larger disruption of the external limiting membrane allows glial cells to migrate out of the retina and to proliferate on the outer retinal surface. Photoreceptor nucleus (P); edge of disrupted external limiting membrane (ELM); subretinal fibrous astrocytes (A). Inset, Light microscopy of the same specimen. A subretinal clump of glial tissue with attachment points to the retina has caused a full-thickness fold of the retina (paraphenylenediamine, phase contrast, ×100). Bar gauge = 1 μ.


P
ELM
A
A


E
L
M
A
R
C
A
S
A

to mature, fibrous astrocytes, whereas cell processes with less cytoplasmic filaments are believed to belong to young, less differentiated astrocytes.

Where the retina was attached to the subretinal tissue the continuity of the external limiting membrane was disrupted. The gap was filled by processes of cells also participating in the formation of the external limiting membrane to either side of the gap. These processes also formed basement membranes, had a smooth endoplasmic reticulum, and contained cytoplasmic filaments. We identified these as outer Müller cell processes (Fig. 9). At larger breaks in the external limiting membrane the participation of outer Müller cell processes in the formation of the subretinal tissue could not be recognized. Fibrous astrocytes outside the retina were connected to the retina by means of heavily interwoven cell processes (Fig. 10).

As the astrocytes migrated out of the retina the shape of their nuclei changed remarkably. Intraretinally, between the photoreceptor nuclei, the nucleus was irregularly indented; whereas in the subretinal tissue, oval to spindle-shaped nuclei were found (Fig. 11).

Autoradiographs after tritiated thymidine injection showed labeling of cell nuclei in the subretinal glial tissue. This indicated DNA synthesis and again demonstrated that the subretinal cells were actually proliferating (Fig. 12).

In preretinal and subretinal glial membranes an extracellular material was often found (Figs. 2, 8, and 11). It consisted of randomly arranged filaments electron microscopically identical to normal collagenous vitreous filaments of the owl monkey eye[6] (Fig. 13).

A peculiar type of extracellular material was found on the retinal side of subretinal glial membranes (Fig. 8, inset) or embedded between these membranes and consisted of parallelly arranged bundles of filaments. The filaments had a variable thickness (maximum: 120 nm) and length but a cross striation with a constant periodicity of approximately 15 nm. At the ends of the bundle and peripherally, the striations were gradually lost, and fine filamentous material without any obvious periodicity was found. Electron microscopically this material was identical to what has been called fibrinoid[7,8] (Fig. 14).

Proliferation of glial cells at the retinal hole—Immediately after producing a retinal detachment by creating a retinal hole there was an open wound in the retina. At this retinal wound pyknotic nuclei in the outer and inner nuclear layers were found. There was also destruction of the outer segments. By the second week, proliferation of cells could be found at the margin of the wound. These cells had pale, round, large nuclei with often prominent nucleoli. A few days later cells with fibrillar cytoplasm and more spindle-shaped smaller nuclei were seen.[5] Electron microscopically, these cells were glial cells. Usually, this reparative process was confined to the wound edge. In some cases, however, progressive proliferation of glial cells occurred. These cells formed membranes that spread over the inner retinal surface (Fig. 15) or formed strands extending into the vitreous cavity along vitreous structures.

Discussion

In experimental retinal detachment in the owl monkey eye we were able to observe the

Fig. 11 (Laqua and Machemer). At the attachment points, the retina (R) and the subretinal membrane (S) appear to be connected to each other mainly by markedly interwoven cell processes. A collagenous material (C) is found in intercellular spaces. The external limiting membrane (ELM) is bent outward. Astrocytes (A) while growing out of the retina show a remarkable variability in the shape of their nuclei. Irregularly indented nuclei, as well as oval and more spindle-shaped nuclei, are seen (same specimen as Figure 7, C). Bar gauge = 1 μ.

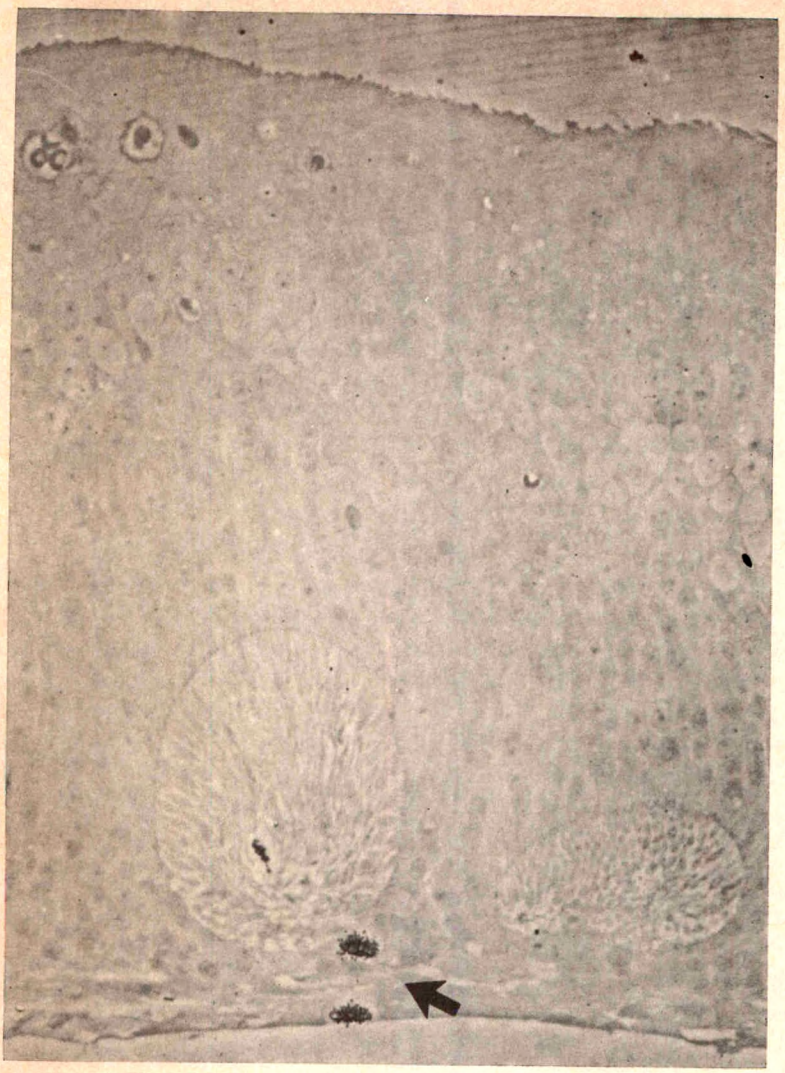


Fig. 12 (Laqua and Machemer). Radioactive labeling of cell nuclei (arrow) in a subretinal glial membrane demonstrates that the cells are actually proliferating (unstained, ×250).

formation of preretinal and subretinal membranes that typically had cellular connections to the retina proper. Based on light microscopic findings we conclude that retinal cells grow out of the retina and build up the preretinal and subretinal tissue. Autoradiography demonstrates DNA synthesis in these cells, confirming that they not only migrate out of the retina but actually proliferate.

Electron microscopically, these cells are identified as glial cells that grow out of the retina through focal interruptions in the internal and external limiting membranes. More specifically, the preretinal and subretinal proliferations consist of astrocytes that show a remarkable variability. As the astrocytes migrate out of the retina and form the preretinal and subretinal proliferations, the shape of their nuclei changes from irregularly indented to oval and spindle shaped. Nuclei of astrocytes migrating out of the retina are larger and have more prominent nucleoli than the nuclei of cells found in the preretinal and subretinal proliferations. The cytoplasm of most of the astrocytes is packed with parallelly arranged filaments, aligned along the axis of the cell. This, together with the fact that a direct connection to the retina can be shown, is the most important feature for their identifica-

tion as mature, fibrous astrocytes.[9,10] In the same tissue, however, cells processes are found that contain fewer cytoplasmic filaments and often more microtubules. These processes are believed to belong to immature, less-differentiated astrocytes.[11]

Some of these cells found in glial membranes and classified as immature astrocytes resemble cell types that are found intravitreally in pigment epithelium proliferations and have been classified there as pigment epithelial cells.[3] This demonstrates that both the retinal astrocyte and the pigment epithelial cell may de-differentiate to such a degree that single cells of this type cannot be identified with certainty even by electron microscopic criteria and can only be classified as cells with neuroepithelial characteristics.

The astrocytes grow out of the retina through a focal interruption in the internal or external limiting membrane. Cell processes are found to protrude through the break but remain attached to and, moreover, seem to contribute to the formation of the internal and external limiting membranes. Except that they contain smooth endoplasmic reticulum, all other cytoplasmic characteristics are similar to those of astrocytes. Because internal and external limiting membranes are formed mainly by Müller cells,

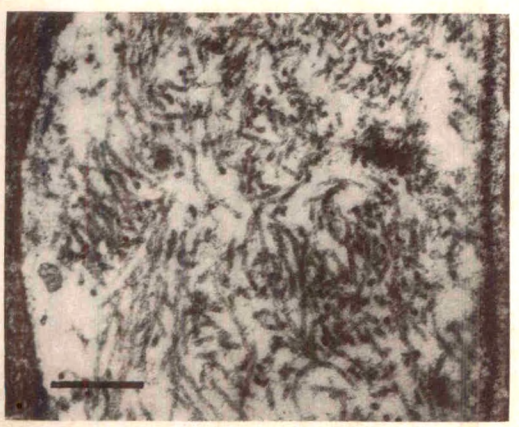


Fig. 13 (Laqua and Machemer). In spaces in preretinal and subretinal glial membranes collagenous filaments are found often overlying a basement membrane (Figures 2, 8, and 11). Bar gauge = 0.2 μ.

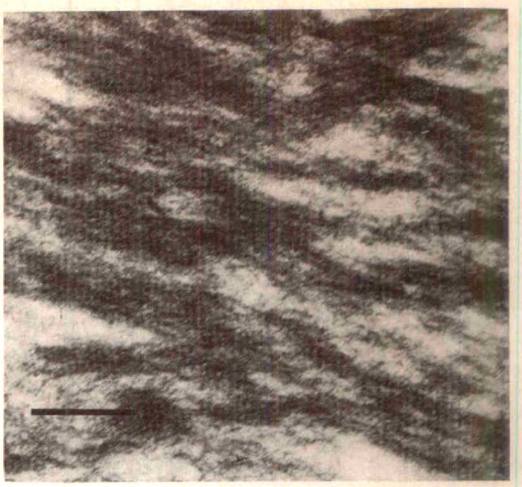


Fig. 14 (Laqua and Machemer). Fibrinoid material is found internal to subretinal glial membranes or embedded in a meshwork of subretinal glial membranes. This material consists of bundles of variable thickness (maximum 120 nm) and lengths, and has a cross striation with a constant periodicity of 15 nm (same specimen as Figure 8, inset). Bar gauge = 0.2 μ.

we conclude these cell processes belong to Müller cells contributing to the formation of the preretinal and subretinal tissue. However, we believe the participation of the Müller cell is confined to the immediate area of the outgrowth. Participation of Müller cells in a glial process has been observed[12,13] and is not surprising, considering Müller cells are a highly specialized type of glial cell[14] and presumably react to the same stimuli as do other glial cells.

The exact stimulus for the proliferation and the outgrowth of glial cells is unknown. Astrocytes react to various stimuli with hypertrophy, multiplication, and fibrosis,[14] whereas Müller cells apparently react only with hypertrophy.[13] This so-called gliosis is believed to be an unspecific reaction and is found as intraretinal gliosis in a large variety of clinical conditions where disintegration of neural tissue occurs.[15,16] However, in some conditions glial cell proliferation is not confined to the retina. An outgrowth of glial cells and preretinal membrane formation may occur and was described as simple epiretinal membranes[17] and surface wrinkling retinop-

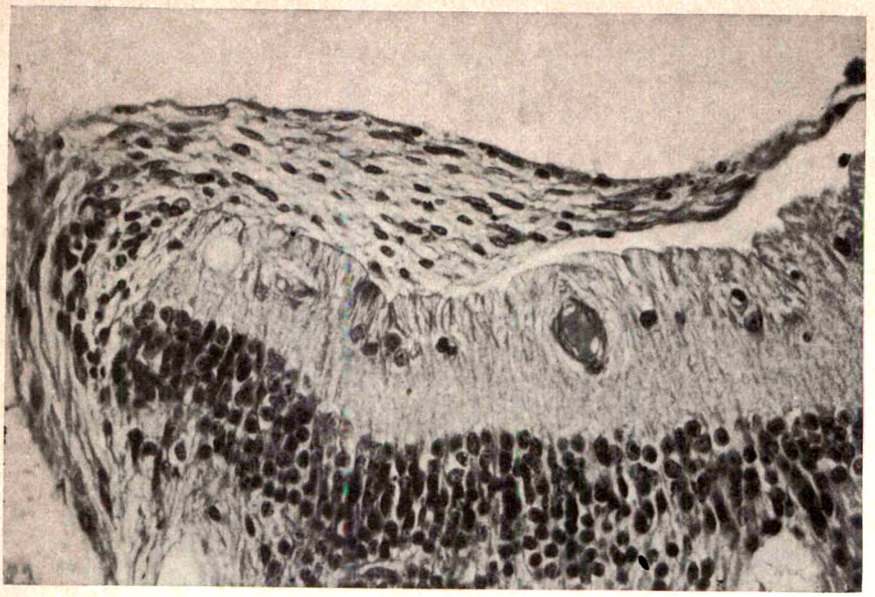


Fig. 15 (Laqua and Machemer). Wound edge of a retinal hole with excessive glial proliferation (PAS, ×250).

athy.[18] Others noted this process in degenerative diseases of the retina,[19] in trauma to the retina,[12] and in developmental conditions.[20] In retinal detachment outgrowth of and membrane formation by glial tissue was probably first mentioned by Leber.[21]

In our material preretinal and subretinal glial proliferation was found as early as four weeks after production of the retinal detachment (Table). However, some of these proliferations which were later proven to be glial in origin were clinically observed as early as three weeks. We found preretinal and subretinal glial proliferation in 45% of the retinal detachments which were four weeks or older. Obviously, glial proliferation is frequent in long-standing retinal detachments; for some reason early glial proliferation (up to three weeks) does not occur. The reason might be that the presumptive stimulus for a glial proliferation—a degeneration of neural elements in the retina—will be fully developed only in a long-standing detachment of a badly nourished retina.[16]

Histologically, this cellular proliferation causes wrinkling of the internal limiting membrane and the nerve fiber layer, or full-thickness folding of the retina. Clinically, starfolds, full-thickness retinal folds, and even a clinical picture similar to what is called massive vitreous retraction (MVR) may be observed.

The mechanism by which glial proliferation causes folding of the retina can be partly explained. Proliferating glial cells often form membranes with a directional component. Parallel orientation of cells and cell processes can be observed which the light microscopist called "isomorphous gliosis" and thought to be a phenomenon secondary to traction.[14] Because the glial cells grow out of the retina primarily without any directional component, the parallel arrangement of the cells must be a secondary phenomenon. We believe that the parallel arrangement is secondary to contraction of the glial cell itself. Recently, it has been shown that cytoplasmic filaments consisting of a contractile actin-like protein are responsible for the contraction of cells and groups of cells.[22,23] Since glial cells contain so many cytoplasmic filaments, we assume they are capable of strong contractions which cause the cells to orient themselves along the main line of traction and result in

a parallel arrangement of the cells. When the membranes are connected to the retina by multiple tissue bridges, the contraction of the proliferating cells is transmitted to the retina, causing it to fold.

Glial proliferation was also observed at the retinal hole and was usually confined to the wound edge. However, in some cases, a progressive proliferation with membrane formation occurred. This suggests that the response of glial tissue to direct trauma may also be excessive.

Embedded in spaces in preretinal and subretinal membranes collagen was found which was electron microscopically identical to vitreous collagen found in the normal owl monkey eye.[6] The presence of this material between glial cells and even in subretinal membranes led us to assume that this was newly formed collagen.[24]

A second extracellular material identical to fibrinoid was found in the subretinal space, either on the retinal side of the glial membranes or trapped between them. Fibrinoid has been seen in a variety of experimental and clinical conditions,[7,8] and there seems to be no doubt that it derives from blood components. Some authors believe that fibrinoid is related to fibrinogen,[7] whereas others strongly feel that it consists mainly of fibrin.[8]

Preretinal and subretinal glial proliferation occurs along with the previously described pigment epithelium proliferation[3] and both are part of the periretinal proliferative process we observed to varying degrees in nearly all retinal detachments. When this proliferative process becomes massive, large areas of the retina may become folded and a clinical picture similar to massive vitreous retraction may develop. To emphasize the importance and ubiquity of cellular proliferations in the development of this condition, we suggest that this condition be called "massive periretinal proliferation" (MPP).

Summary

In experimental retinal detachment of the owl monkey we observed the formation of preretinal and subretinal membranes which had cellular connections to the retina proper. Based on light microscopic findings we concluded that retinal cells grow out of the retina and build up the preretinal and subretinal tissue. Electron microscopically these cells are identified as astrocytes which grow out through focal interruptions in the internal or external limiting membrane. In the immediate area of outgrowth Müller cell processes participate in the formation of the preretinal or subretinal tissue. These glial membranes can cause wrinkling of the internal limiting membrane and the nerve fiber layer or full-thickness folding of the retina. Glial proliferation plays an important role in the development of a complication in retinal detachment which we suggest calling "massive periretinal proliferation" (MPP).

Acknowledgments

We thank Mrs. M. Halley for histology and electron microscopy; Mr. B. Davis for electron microscopy; Mr. E. Reeves and Mr. W. Hinecker for their help in the animal experiments; Ms. B. French for photography; W. Benson, M.D., and Mrs. R. Hurtes for editorial assistance; and Mrs. C. Rowlette for secretarial assistance.

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FIBROUS HISTIOCYTOMA OF THE CORNEOSCLERAL LIMBUS

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Fibrous histiocytoma of the ocular tissues is an uncommon tumor that has only recently gained specific recognition.[1-10] Although fibrous histiocytomas of the orbit are often aggressive,[4] those involving only the eyelid and epibulbar tissues are characteristically benign.[1,6] Previous reports of such tumors affecting the conjunctiva or corneoscleral limbus, or both, are apparently limited to only two cases.[1,6] We report the clinical, histopathologic, and ultrastructural findings in an additional case of fibrous histiocytoma that developed at the corneoscleral limbus of a 21-year-old white woman.

CASE REPORT

This 21-year-old white woman was initially seen on May 20, 1974, for evaluation of a mass lesion at the inferotemporal corneoscleral limbus of the left eye that had progressively enlarged for two months. The patient's past medical and ocular history was noncontributory, except for a childhood accident of blunt trauma to the left upper eyelid that had required sutures.

Initial therapy for the limbal lesion consisted of prednisolone ⅛% ophthalmic drops for one week, four times daily, that had no apparent effect. Accordingly, in August, the patient was hospitalized for excisional biopsy of the lesion. At that time, visual acuity was 20/20 in both eyes, with insignificant refractive error. On external examination, a small well-healed cutaneous scar was evident in the left upper eyelid fold. A raised, yellowish-tan lesion, measuring approximately 5 mm in diameter (unchanged from previous examination), was situated at the corneoscleral limbus from 3 to 7 o'clock, extending centrally approximately 3 mm and peripherally confluent with the conjunctiva (Fig. 1). Multiple superficial conjunctival blood vessels radiated into the lesion. On gonioscopic examination, the tumor showed stromal invasion without penetration of Descemet's membrane, although the entire cornea was bowed posteriorly. No abnormalities of the anterior chamber and angle were visible. Intraocular pressures and ophthalmoscopic examination were unremarkable.

General physical examination revealed only obesity. Specifically, we detected no organomegaly, cutaneous lesions, or skeletal abnormalities. Laboratory studies included the following values: hemoglobin, 13.6 g/100 ml; hematocrit, 40%; white blood cell count, 6,700/mm^3; normal serum blood chemistries (calcium, inorganic phosphorus, glucose, urea nitrogen, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase); and normal urinalysis, syphilis serology, and thyroid function (T_3 and T_4) tests. In addition, total serum cholesterol (202 mg/100 ml), triglycerides (72 mg/100 ml), and lipoprotein electrophoresis tests were entirely within normal limits.

On Aug. 19, an incomplete excisional biopsy of the lesion revealed a fibrous histiocytoma. During the next two months, the lesion gradually increased in size, and on Oct. 11, complete excision was accomplished by lamellar keratectomy and sclerectomy with application of cautery and cryotherapy to the bed of the lesion. No indication of recurrence of the lesion was apparent during a five-month follow-up period.

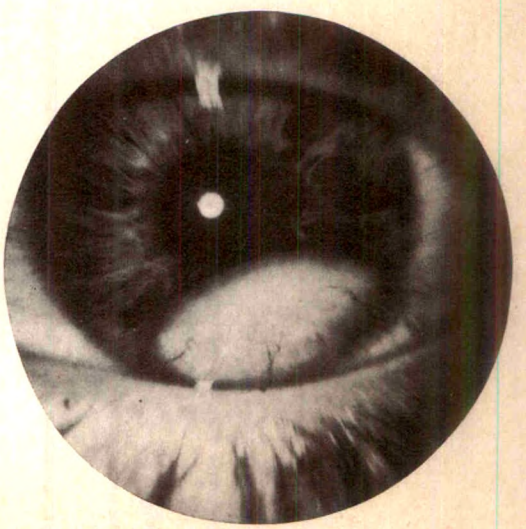


Fig. 1 (Faludi, Kenyon, and Green). Clinical appearance of tumor shows elevated limbal mass extending from bulbar conjunctiva into clear cornea. Note superficial conjunctival vessels coursing over lesion.

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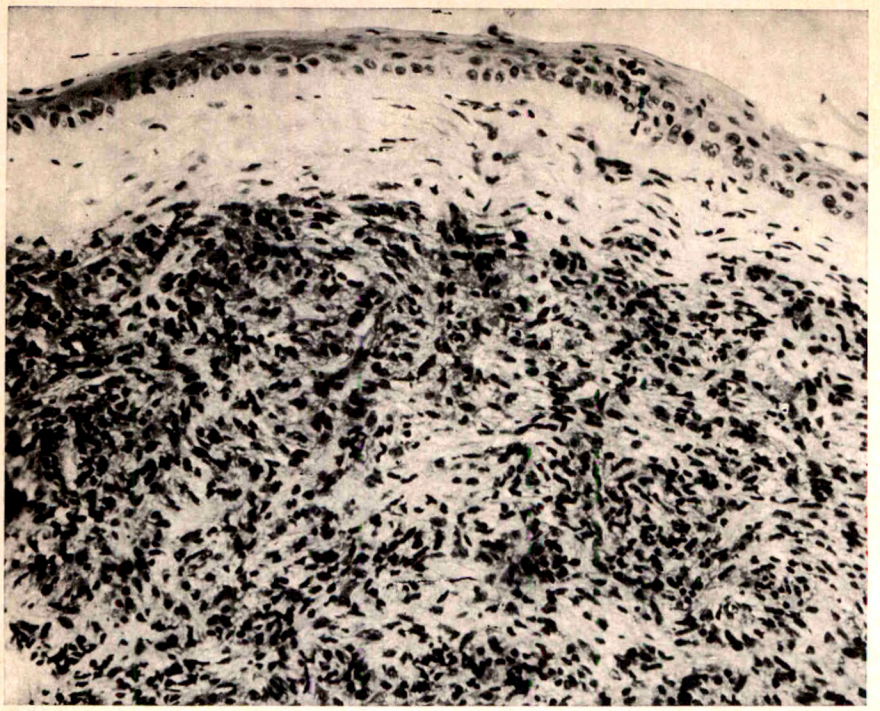


Fig. 2 (Faludi, Kenyon, and Green). Survey light photomicrograph demonstrates dense cellular composition of tumor invading superficial corneal stroma. The corneal epithelium and Bowman's membrane appear essentially uninvolved (hematoxylin-eosin, ×220).

Material and methods

The entire specimen obtained by excisional biopsy and most of the specimen from the complete excision were prepared for routine histopathologic and histochemical study. Stains performed included hematoxylin-eosin, PAS, Masson's trichrome, phosphotungstic acid-hematoxylin (PTAH), Wilder's reticulum, Prussian blue, Alcian blue (pH 2.5), colloidal iron, Giemsa, oil red O, and Sudan black B. Additional segments of the second specimen were prepared for electron microscopy by immediate fixation in 0.5% glutaraldehyde-2% formalin, post-fixation in 2% osmium tetroxide, dehydration in graded alcohols, and impregnation with Araldite epoxy resin. Thick sections were stained with paraphenylenediamine (PPDA) for phase contrast photomicrography. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with a JEM 100-B electron microscope.

Results

By light microscopy, the tumor appeared to be a densely cellular, localized, unencapsulated mass confined to the subepithelial connective tissue of the corneoscleral limbus and peripheral cornea (Fig. 2). An infiltrate of chronic inflammatory cells was present in the periphery of the tumor and extended superficially toward the epithelium in some areas. More centrally, however, we encountered plasma cells and lymphocytes less frequently as the bulk of the tumor consisted predominantly of two cell types: large histiocytic cells with foamy vacuolated cytoplasm (Figs. 3 and 4, inset), and smaller, fibrocytic cells occasionally arranged in a cartwheel or storiform configuration (Fig. 5). We did not observe giant cells, abnormally numerous mitotic figures, or cellular dysplastic changes. The basal margin of the specimen was infiltrated with tumor cells. Special histochemical stains were positive

only with respect to reticulum staining of the fibrous interstitium and lipid staining (with Sudan black B and oil red O) within the cytoplasm of the histiocytes.

Electron microscopy confirmed the identity of the two major cellular constituents. The histiocytic cells (Fig. 4) were large epithelioid cells characterized by lobulated nuclei with marginated chromatin, irregularly ruffled plasma membranes with interdigitating processes, and numerous small (approximately 1 to 2 μ in diameter) intracytoplasmic vacuoles with pleomorphic contents (predominantly neutral lipid of varying saturation, corresponding to that demonstrable by histochemical lipid stains). Moderate amounts of rough-surfaced endoplasmic reticulum and occasional mitochondria were present incidentally. The fibrocytic cells (Fig. 6), in contrast, were fusiform in configuration with ellipsoid nuclei, considerable endoplasmic reticulum, and extended cytoplasmic processes. The cell membrane was often closely associated with the randomly arrayed collagenous fibers of uniform diameter (approximately 35 nm) that comprised the interstitial substance of the tumor (corresponding to the fibrillar material histochemically visualized with reticulum stain).

Discussion

This 21-year-old woman, with no evidence of systemic disease, had a fibrous histiocytoma at the corneoscleral limbus. The clinical behavior of the enlarging tumor, with no evidence of recurrence several months after excision, suggests its benign character. The histopathologic[1,6] and ultrastructural[11] features of the tumor are typical, as it consists of lipid-containing histiocytes and fibrocytic cells arranged in a storiform pattern with a collagenous interstitium.

Fibrous histiocytomas involving the ocular tissues have received increasing interest in recent years.[1–9] Both clinically and histopathologically, a spectrum of findings has been observed. Usually these tumors appear as solitary, locally confined lesions. As they affect the corneoscleral limbus or conjunctiva, their behavior is entirely benign,[1] and it is not clear whether they represent a reactive or a true neoplastic process.[10] In the orbit,

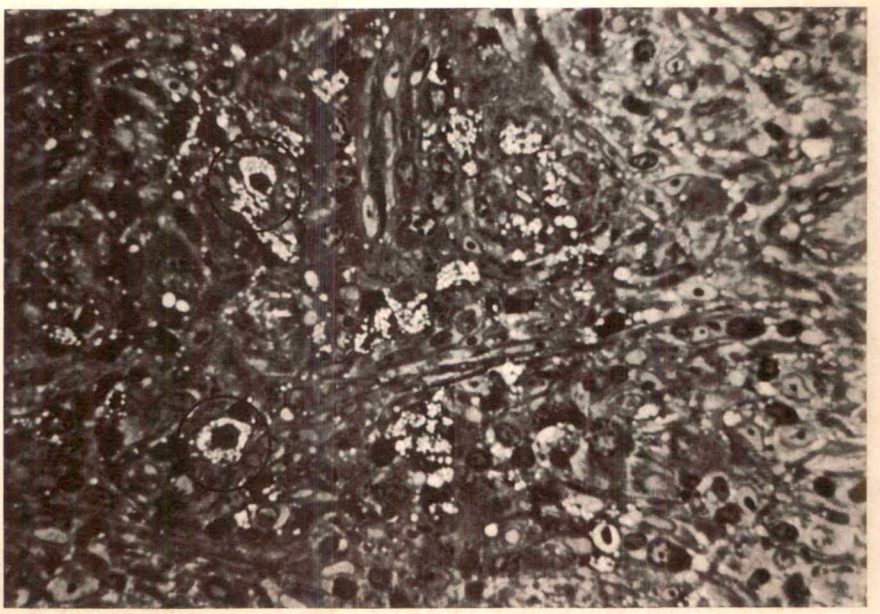


Fig. 3 (Faludi, Kenyon, and Green). Phase contrast photomicrograph of central tumor illustrates many histiocytic cells (circled) with finely vacuolated cytoplasm interspersed among cords of fibrocytic cells (PPDA, ×750).

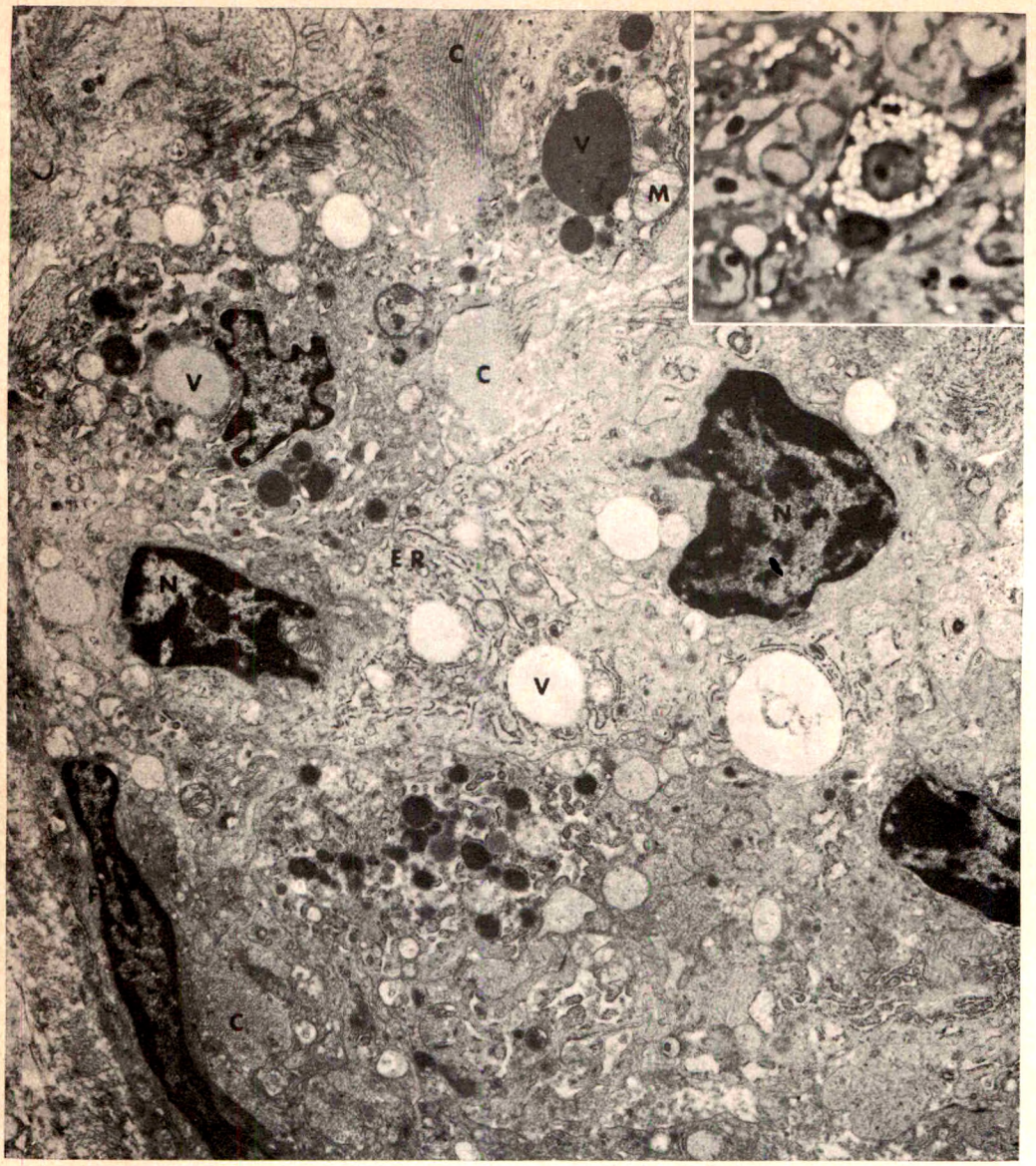


Fig. 4 (Faludi, Kenyon, and Green). Inset, Phase contrast photomicrograph displays extensive cytoplasmic vacuolation of histiocytes (PPDA, ×1,800). Electron micrograph of adjacent area shows predominantly histiocytic cells with characteristic irregular nuclear profiles (N), pleomorphic intracytoplasmic vacuoles containing lipid of variable saturation (V), moderate rough-surfaced endoplasmic reticulum (ER), and incidental mitochondria (M). Fibrocytes (F) are interspersed within the collagenous interstitum (C) ×7,600).

however, they may demonstrate malignant tendencies, although metastatic spread has not been observed.[4] Multiple lesions may also occur, as Albert and Smith[6] demonstrated in a patient with several fibrous xanthomas of the conjunctiva and skin with no evidence of systemic disease. Multiple lesions, of course, increase suspicion that they are the superficial manifestation of a systemic reticuloendotheliosis, such as Hand-Schüller-Christian or Gaucher's disease. Differences in the histopathologic appearance of such tumors were also encountered, ranging from the predominantly histiocytic character of

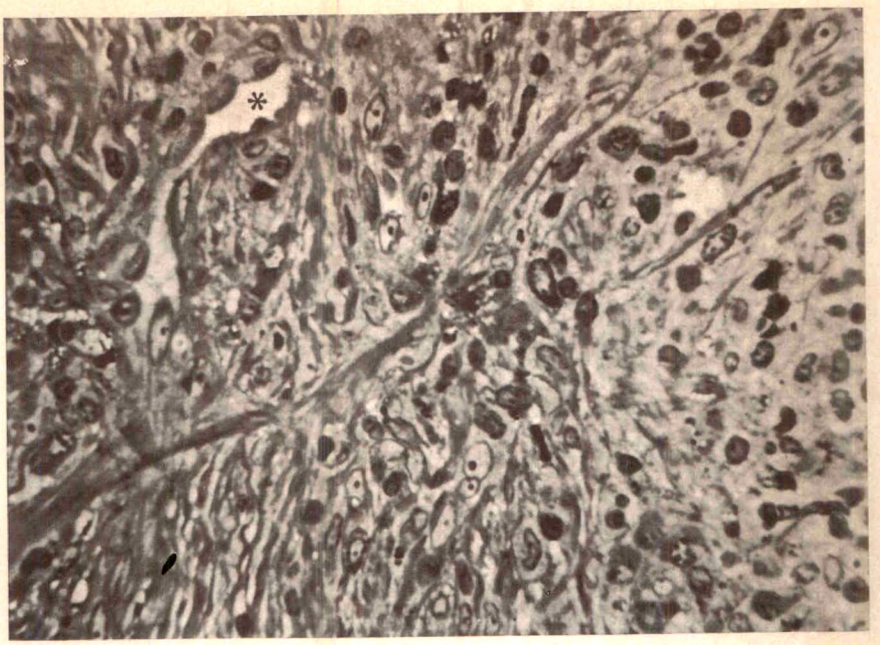


Fig. 5 (Faludi, Kenyon, and Green). Phase contrast photomicrograph of central tumor demonstrating radiating storiform configuration of fibrocytic cells. Occasional small blood vessels (*) and histiocytes are evident (PPDA, ×750).

xanthelasma and systemic xanthomatoses, to the mixed populations of histiocytes and fibrocytes here, and to almost exclusively fibroblasts as in fibromas of the conjunctiva and dermatofibromas of the skin.

The present concept of fibrous histiocytoma evolved from the demonstration that in tissue culture, histiocytes can behave morphologically as fibroblasts.[12] Conversely, the ability of fibrocytic cells to accumulate intracytoplasmic lipid in vitro was also observed.[13] Thus, the morphology of fibrohistiocytic tumors may reflect the degree to which the component cells have exercised their fibrocytic or histiocytic potential. Additional variations among these tumors may



Fig. 6 (Faludi, Kenyon, and Green). Electron micrograph shows a fibroblastic cell process (F) possibly engaged in the production of randomly arranged native-banded collagen fibrils (C), approximately 35 nm in diameter (×16,000).

also occur, depending on their collagen and reticulin content, lipid composition, cellular organization, and mitotic activity.

Summary

A 21-year-old white woman had an apparently benign fibrous histiocytoma at the corneoscleral limbus. By histopathologic and ultrastructural studies, the tumor consisted of lipid-containing histiocytes and fibrocytic cells arranged in a storiform configuration with a collagenous interstitium. After an excision, the lesion gradually decreased in size and did not recur in a five-month follow-up period.

Acknowledgment

We thank Allen E. Silver, M.D., for permission to report this case.

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THE PLEOMORPHISM AND COMPLICATIONS OF POSTERIOR HYPERPLASTIC PRIMARY VITREOUS

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Persistent hyperplastic primary vitreous is believed to be the result of anomalous development of the secondary vitreous with associated hyperplasia of mesodermal elements of the primary vitreous-hyaloid artery complex. In recent years, two clinical forms have been recognized (Table 1). Both types are usually unilateral and are seen in patients who were of normal gestational age and birth weight and received no perinatal oxygen. Reese[1] extensively investigated anterior hyperplastic primary vitreous. It was formerly known as persistent tunica vasculosa lentis and principally affects the anterior segment, often presenting as leukokoria in a small turned eye. Posterior hyperplastic primary vitreous[2-4] has previously been called congenital retinal septum or ablatio falciformis congenita. A retinal fold is commonly seen in the posterior variety, along with other anomalies that constitute the syndrome.[4]

There is great variability in the expression of both anterior and posterior hyperplastic primary vitreous. Some eyes show minimal manifestations; others have severe involvement with secondary complications; and intermediate types, with both anterior and posterior defects, have been reported. I describe the observed pleomorphic forms in a series of patients with posterior hyperplastic primary vitreous.

METHODS

I studied 30 white patients, 13 males and 17 females. Examinations included measurement of visual acuity and Schiøtz tonometry. Fundus studies were performed by binocular indirect ophthalmoscopy with scleral depression and supplemented by photography in some cases. In young patients, the examinations were conducted under general anesthesia and all findings were recorded on large fundus drawings. Slit-lamp studies of the anterior segment were done using a Haag-Streit instrument, model 900. When age and cooperation permitted, detailed vitreous examinations were performed using a Goldmann three-mirror lens, and the data were illustrated on Tolentino diagrams.

RESULTS

The patients were first examined at various ages, from childhood to age 23. The average age when the diagnosis was made was 6 years. Twenty-five of the 30 patients were affected unilaterally, and both eyes were involved in five. Among the 35 affected eyes there were 16 right eyes and 19 left eyes. The most common presenting complaints were poor vision and strabismus. Visual acuity varied from 20/25 to light perception, but in 21 of the 35 eyes, visual acuity was 20/200 or less. Seven additional eyes probably had visual acuity of less than 20/200, but the patients were too young to test. Strabismus was found in 20 of the 30 patients; 12 esotropic and eight exotropic deviations were noted.

TABLE 1

PERSISTENT HYPERPLASTIC PRIMARY VITREOUS

Anterior	Posterior
Microphthalmos	Microcornea
Retrolental fibrovascular membrane	Vitreous membranes
Ciliary processes drawn centrally	Retinal fold (any meridian)
Persistent hyaloid artery	Hyaloid artery remnants along fold

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This study was supported by Public Health Service grant EY-00227 from the National Eye Institute, National Institutes of Health.

Presented in part before the Seventh Scientific Meeting of the Retina Society, Sept. 13, 1974, Montreal, Quebec.
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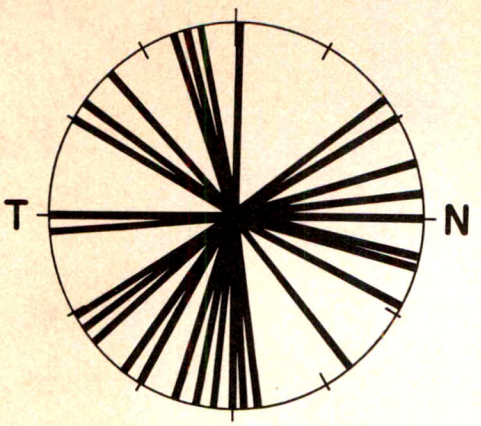


Fig. 1 (Pruett). Meridional distribution of vitreous bands in 29 eyes; T indicates temporal; N, nasal.

Nystagmus was observed in all five patients affected bilaterally.

Horizontal measurements of the corneal diameters had been recorded in 28 patients. Thirteen patients had relative microcornea (1.0 to 1.5 mm smaller); in 15 patients the corneal diameters were equal. Gonioscopy, performed on 23 patients, revealed a "juvenile" angle with multiple iris processes in the affected eye in 11 patients and a normal angle in the other 12. When seen initially, the lens was clear in 31 eyes although seven of these showed a Mittendorf dot with ghost remnants of the tunica vasculosa lentis, and one developed mild cataractous changes over several years. Lens opacification in four eyes made indirect ophthalmoscopy difficult in two eyes and impossible in two others. Dense cataracts were found in one eye each of two bilaterally but asymmetrically involved sisters who had nystagmus. These children showed predominantly posterior manifestations in the fellow eye, and they were the only examples of familial incidence. There were two eyes in the series with subluxation of the lens and one with a lens coloboma in the meridian of a retinal fold.

Vitreous membranes, usually extending from the disk toward the equatorial zone or anteriorly to the region between the ora serrata and the lens equator, were a universal finding. Among the 33 eyes in which ophthalmoscopy was possible, 29 had membranes that were radially oriented. The anterior extension of the membranes frequently fanned out and extended circumferentially for variable distances and there appeared to be no meridian that was preferentially involved (Fig. 1). A retinal fold, of variable prominence, was associated with radial vitreoretinal traction bands in 23 of these 29 eyes. Four other eyes showed multiple vectors of vitreoretinal traction.

Ten of the 33 eyes in which the fundus was visualized showed no retinal fold. In these, remnants of primary vitreous and hyaloid arterial system were attached to the disk and posterior pole with anterior extensions into the vitreous gel toward the lens. In its mildest form, mesodermal remnants were seen over the disk with slight elevation of the peripapillary retina and minimal disturbance of the macula (Fig. 2). Slightly more advanced cases showed fibrous extensions from the disk inserted on the peripapillary retina and retinal vessels (Fig. 3). A summary of the

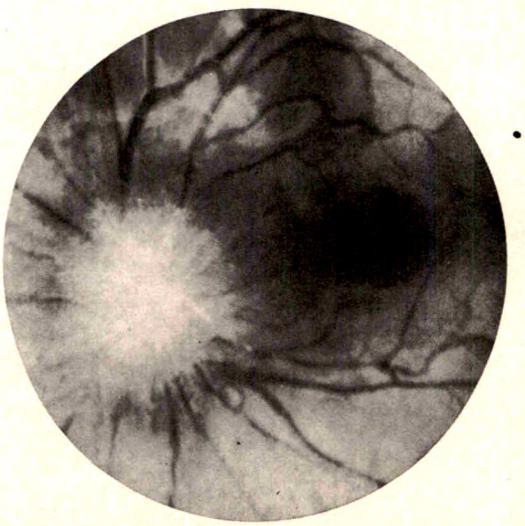


Fig. 2 (Pruett). Minimal expression of posterior hyperplastic primary vitreous observed in one eye of an 8-year-old girl. Mesodermal elements were present anterior to the disk and extended into the vitreous cavity. The peripapillary retina was elevated but the macula was undisturbed and visual acuity was 20/20. The corneal diameters were equal and the filtration angles were normal.

clinical findings in this series is presented in Table 2.

Complications—The morbidity was high and the retina suffered the most in this group of patients (Table 3). The macula was pigmented, dragged, or involved by a retinal fold in 23 eyes, and in 15 eyes there was some degree of retinal detachment. Retinal problems probably were present in the two eyes with extensive lens opacifications. Vitreous hemorrhage due to vitreoretinal traction and leakage from retinal blood vessels was seen in one eye. Unilateral open-angle glaucoma was detected and successfully treated medically in another eye with a long-term retinal detachment that had reattached spontaneously.

Of the 15 eyes with retinal detachment, five were extensive and one required an operation (Table 4). This detachment occurred in a unilateral case with an inferior temporal retinal fold. Repair of the detachment required four scleral bucklings and supplementary photocoagulation over the buckled area. In the last operative procedure, a posterior wedge-shaped implant was used. This extended under the retinal fold, and included

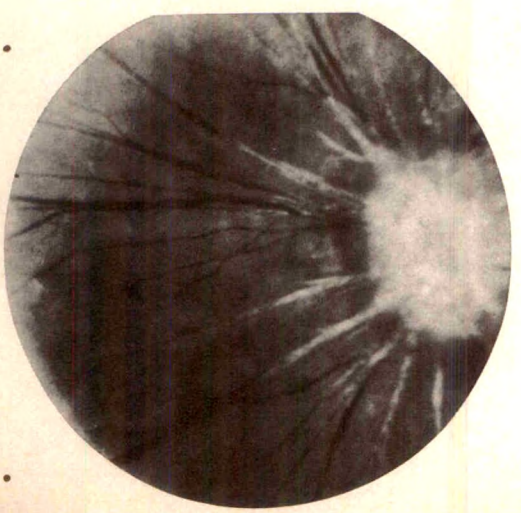


Fig. 3 (Pruett). A slightly more advanced form of hyperplastic primary vitreous in a 17-year-old girl. Radial extensions of mesodermal tissue over the disk inserted into the peripapillary retina and along the retinal vessels. Visual acuity was 20/25.

TABLE 2

CLINICAL FINDINGS OF POSTERIOR HYPERPLASTIC PRIMARY VITREOUS

	Observed	Total	%
	Patients		
Unilateral	25	30	83
Bilateral	5	30	17
Strabismus	20	30	67
Nystagmus	5	30	17
	Eyes		
Vision ≤ 20/200	28	35	80
Microcornea	13	28	46
Immature angle	11	23	48
Clear lens	31	35	89
Vitreous membranes			
Radial	29	33	88
Multiple	4	33	12
Retinal traction			
Fold	23	33	70
Disk	10	33	30

TABLE 3

POSTERIOR HYPERPLASTIC PRIMARY VITREOUS COMPLICATIONS

	Observed Eyes	Total	%
Macula, pigmented, dragged, involved by fold	23	33	70
Retina, detached	15	33	45
Vitreous hemorrhage	1	33	3
Cataract, fundus obscured	2	35	6
Glaucoma, open-angle	1	35	3

TABLE 4

MANAGEMENT OF RETINAL DETACHMENT IN 15 EYES

	No. of Eyes
Extensive detachment	5
Subtotal, stable, not operated	(1)
Delayed spontaneous reattachment	(1)
Reattached by scleral buckling (4 times) and photocoagulation	(1)
Inoperable due to MPR*	(2)
Posterior detachment	10
Stable, not operated	(9)
Progressive, responded to vitreous stalk sectioning	(1)

* Indicates massive preretinal retraction.

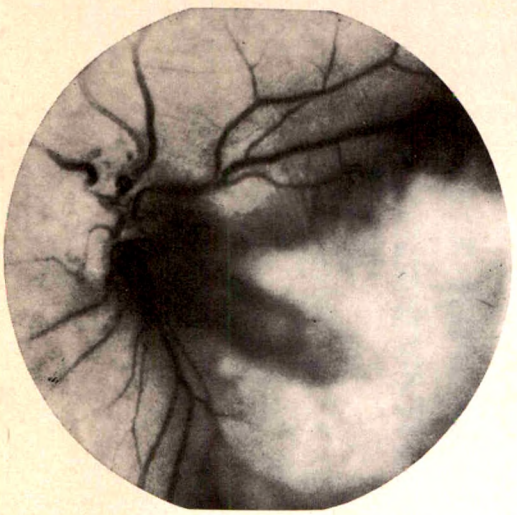


Fig. 4 (Pruett). Four scleral bucklings and supplementary photocoagulation were required to repair an extensive detachment of the retina in this 23-year-old man. A radial scleral buckling extends posteriorly beneath a retinal fold in the lower temporal quadrant of the left eye.

the macula (Fig. 4). The resulting visual acuity was 20/400; it had been 20/40 before the retinal detachment occurred. In another patient a stable peripheral traction detachment has been observed without intervention. Another patient, followed for many years, showed spontaneous reattachment and degeneration of the lower half of the retina that had been detached. In two eyes, the retinal detachment was total, complicated by massive preretinal retraction, and considered inoperable.

There were ten eyes in which the retinal detachment was limited to the posterior pole and surrounded the disk. Nine of these were stable and an operation was not necessary. In one eye, the detachment progressed over a 12-month period of observation. Sectioning of the vitreous stalk with scissors was successful and the retina settled back into position (Fig. 5).

Discussion

Diagnosis of posterior hyperplastic primary vitreous may be difficult because the fundus findings may mimic those of retrolental fibroplasia. The causes of secondary retinal fold must also be ruled out (chronic

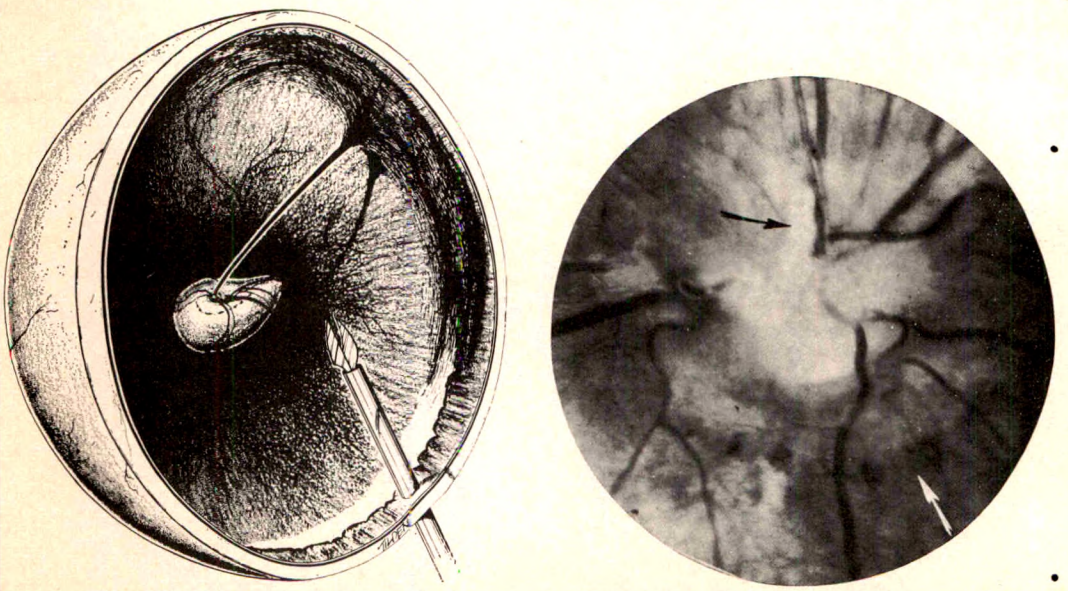


Fig. 5 (Pruett). A retinal detachment at the posterior pole in this 6-year-old girl progressed over a 12-month observation period. Left, A vitreous stalk was sectioned by scissors inserted through an incision in the pars plana ciliaris. Right, A remnant of the severed stalk (black arrow) was seen extending from the disk into the vitreous cavity postoperatively but the retina had settled back into position. A pigmented demarcation line (white arrow) indicates the boundary of the detachment before extension occurred.

uveitis, parasite, and occult intraocular foreign body). These can often be eliminated by a detailed history, ancillary medical studies, and a meticulous examination of both eyes. General anesthesia is often required since many of the patients are children. A contributory history including full-term gestation with normal birth weight, no perinatal oxygen administration, no history of ocular trauma or chronic uveitis, and no family pets favors the diagnosis of posterior hyperplastic primary vitreous. A normal eosinophil count and the absence of an intraocular foreign body on x-ray film would also support the diagnosis. The retinal fold, if present, is usually unilateral and can occur in any meridian. Any or no refractive error may be present (myopia is common in retrolental fibroplasia). If other signs of anomalous development are observed, this further substantiates a prenatal rather than postnatal etiology. One should search carefully for relative microcornea, an immature angle structure, and hyaloid artery remnants behind the lens and within the vitreous cavity. The optic nerve may, in some cases, be hypoplastic and the retinal vessels may fail to extend anterior to the equator in posterior hyperplastic primary vitreous. Lens subluxation or lens coloboma are also significant since these defects can occur with anomalous development of the vitreous.[5]

Once the diagnosis is established beyond a reasonable doubt, patients are advised to return for regular follow-up examinations. If retinal detachment occurs, earlier diagnosis is then more likely in these eyes which may already have poor vision. As the methods of vitreous surgery become more sophisticated, a better prognosis may be offered to these patients in the future.

Summary

Among 30 patients examined, posterior hyperplastic primary vitreous was monocular in 25 and binocular in five. Poor vision and strabismus were the most common presenting complaints. All patients had vitreous membranes usually extending from the disk toward the equatorial zone. In 70% of the affected eyes, the vitreous membranes were associated with a radial retinal fold. Macular function was disturbed in 70% and retinal detachment was observed in 45% of the eyes. One extensive retinal detachment was successfully treated by scleral buckling; another detachment, limited to the posterior pole, responded to sectioning of a vitreous band with scissors.

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PIGMENTED PARAVENOUS RETINOCHOROIDAL ATROPHY

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In 1962, when writing about pigmented paravenous retinochoroidal atrophy, Franceschetti[1] said "A rare affection often becomes less rare when given an appropriate name . . . in the hope of attracting attention . . . to elucidate (its) etiology by a greater number of observations." While we feel reasonably certain that similar cases have been recognized and correctly diagnosed, this seems to be the first report of a series of patients in this country having this unusual degeneration, in which zones of retinochoroidal atrophy characteristically follow the distribution of the major retinal vessels.

CASE REPORTS

Case 1—A 27-year-old white man, seen in consultation in March 1974, complained of mild pain and decreased vision in the right eye of two weeks' duration. He noted involuntary closure of the right upper eyelid for approximately the same period of time. There was no family history of a similar disorder and no consanguinity in the genetic background. The patient had the usual childhood illnesses. Careful review of symptoms revealed mild photopsia, more marked on the right side.

The corrected visual acuity was R.E.: 20/30-2, and L.E.: 20/20. External examination and slit-lamp findings were normal. Inspection of the fundus through dilated pupils revealed atrophic contiguous lesions, approximately 1 disk diameter in size, surrounding all major venous arcades (Fig. 1). The lesions were bilaterally symmetrical. Minimal pigment deposition was seen along the venous walls immediately adjacent to the atrophic paravenous areas. Perimetry studies revealed an enlarged blind spot in the left eye, and a significant constriction of the peripheral fields of both eyes, more marked on the right side (Fig. 2). Fluorescein angiography demonstrated a window defect of choroidal atrophy with the hyperfluorescence characteristic of retinal pigment epithelial degeneration (Fig. 3). There was no evidence of fluorescein leakage beneath or within the neural epithelium at any stage of the angiogram. Color vision tests made with the H-R-R and Ishihara pseudoisochromatic plates were completed without error. Dark adaptometry was performed with a 1-degree test object located 15 degrees superior to fixation. Using a stimulus flashing on and off at one-second intervals, there was a normal onset of the cone portion of the curve, together with a normal development of the rod portion. The final rod threshold at 45 minutes was 1.0 log units above normal (Fig. 4).

The electroretinographic (ERG) studies were made in our routine manner. After dark adaptometry, patients were dark adapted for an additional 45 minutes. Burian-Allen contact lens electrodes were inserted under red light illumination after the instillation of proparacaine hydrochloride 0.05% ophthalmic solution for corneal anesthesia. White light stimuli of 20-msec duration recorded single and multiple flash responses. Patients with dark-adapted eyes under Maxwellian view received the flashes via optical fibers from a tungsten lamp, with a Hartline shutter and a series of neutral density filters to vary stimulus intensity. Threshold responses were measured, beginning with subthreshold stimuli in single flashes.

After a lapse of approximately 30 seconds, the next flash was presented. As the stimulus intensity increased, the interval between single flashes lengthened to approximately one minute to insure the preservation of the dark-adapted state. Multiple flash (flicker) studies at the conclusion of each testing session determined critical flicker fusion (CFF) values. The ERG responses were markedly abnormal in each eye. The first test yielded barely recordable b-waves of low amplitude (20 μV). A second test, obtained eight months later, demonstrated nonrecordable b-waves to single flashes of light.

Case 2—A 4-year-old white boy seen on routine preschool examination presented no specific ocular or visual complaints. Examination revealed normal visual acuity in each eye and fundus features similar to those seen in Case 1, consisting of bilaterally symmetrical pigmented paravenous retinochoroidal atrophic changes. Because the patient was young, it was difficult to document the fundus picture by fluorescein fundus photography, or to perform any of the retinal tests employed in Case 1. The highly characteristic fundus appearance, however, identified the condition.

Case 3—A 47-year-old man, seen in consultation in May 1974, had loss of central vision in the left eye since 1962, and the right eye since 1964. He complained also of headaches, photopsia, and of seeing halos around lights. He had been examined many

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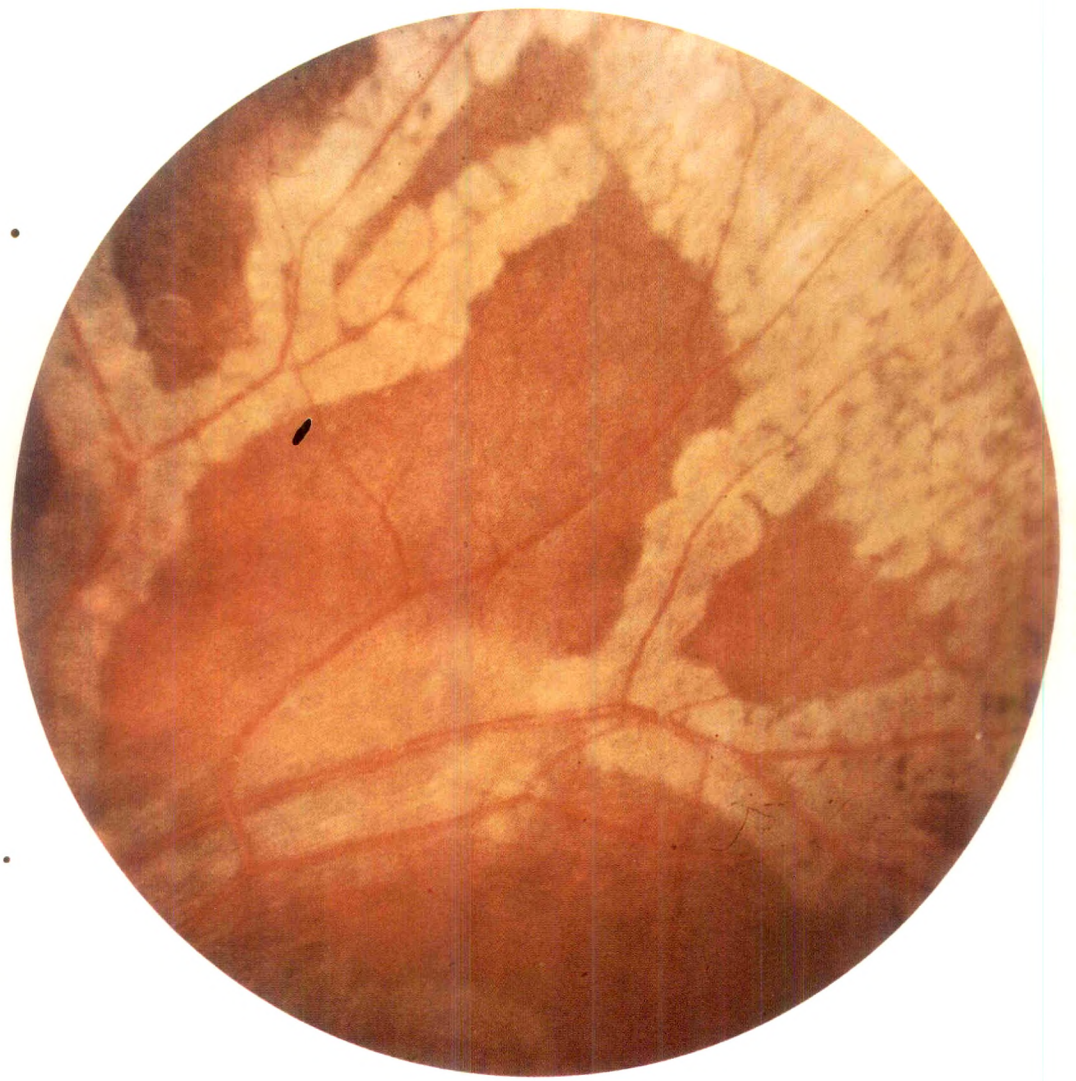


Fig. 1 (Pearlman and associates). Typical contiguous atrophic retinal pigment epithelial lesions along the distribution of the major venous arcades.

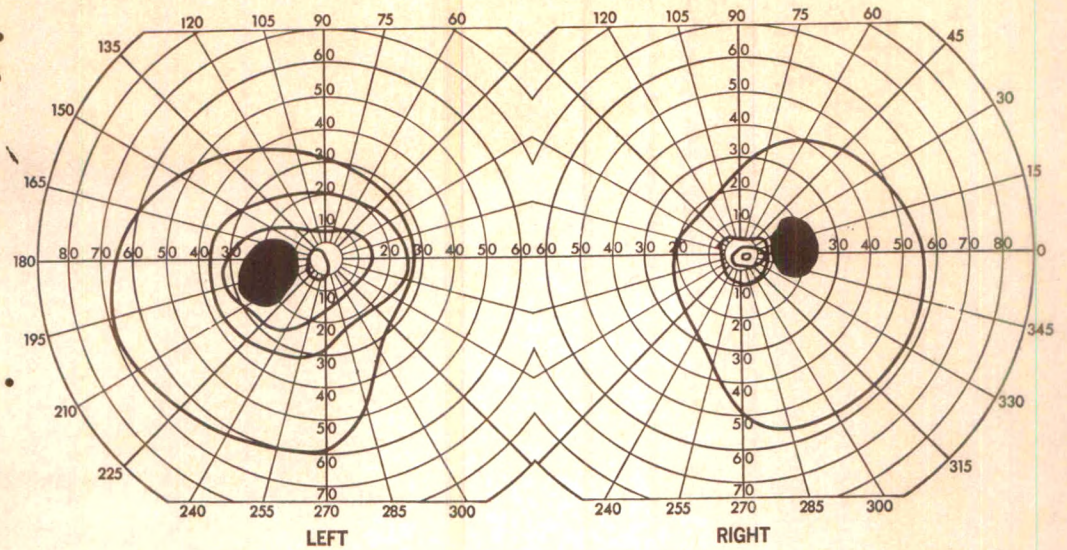


Fig. 2 (Pearlman and associates). Goldmann fields showing constriction of inner isopters in both eyes, marked in right eye with an enlarged blind spot in the left eye. The largest isopter represents the IV_4 stimulus on the Goldmann perimeter; the next largest is the I_4 stimulus; the next is the I_2 setting; and the smallest isopter is the I_2 stimulus setting.

times and was thought to have a variant type of pigmented paravenous retinochoroidal atrophy. He had a noncontributory ocular family history and a review of his medical history indicated that he had not undergone treatment for any serious illnesses.

His best visual acuity was R.E.: 20/200, L.E.: hand motions. External examination revealed no significant abnormality in either eye. Slit-lamp findings, including applanation tonometry, were normal. Ophthalmoscopic examination of the fundus through dilated pupils showed extensive pigmented paravenous retinochoroidal atrophy involving both eyes, with extensive bilateral posterior pole retinal degeneration.

Discussion

Few cases of this rare but most characteristic condition have been described. Brown[2] described the condition as "retino-choroiditis



Fig. 3 (Pearlman and associates). Window defect of the retinal pigment epithelium along venous branches. No leaks of dye were noted beneath or into neurosensory retina. Left, more central, while right is more peripheral and shows greater involvement farther out in the fundus.

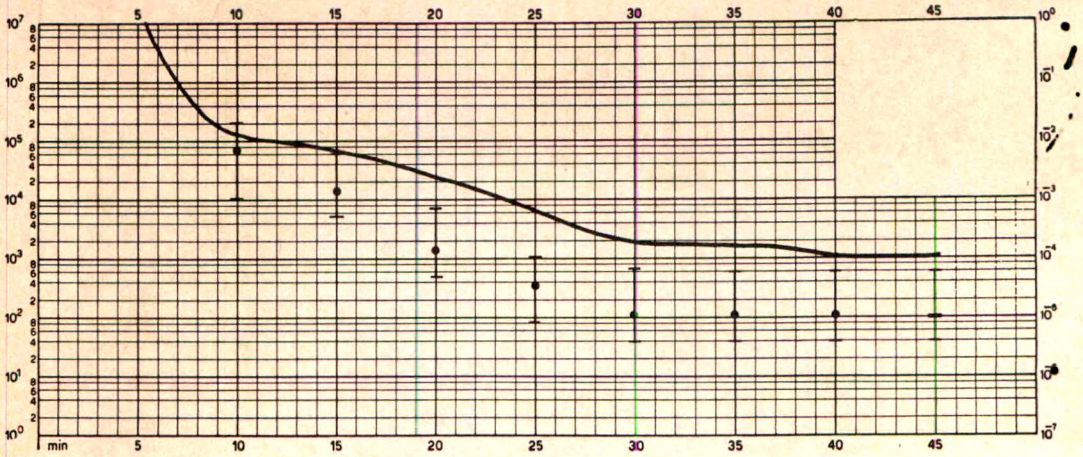


Fig. 4 (Pearlman and associates). Dark adaptation curve showing elevation of final rod threshold at 45 minutes by 1 log unit. This indicates a clinically significant degree of night vision disturbance. The dots and bars indicate the mean normal value for the laboratory ± 2 S.D.

radiata." Kraffel[3] used the same descriptive title in 1955. Bücklers[4] described a similar case and referred to it as pseudoretinitis pigmentosa following measles. Morgan,[5] observing the same clinical entity, called it congenital pigmentation of the retina. Brognoli[6] referred to it as melanosis of the retina, while Weve[7] named it paravenous retinal degeneration. In a review in 1962, Franceschetti[1] commented that a case of Hsin-Hsiang's,[8] among others, suggested a primary pathologic process, rather than a secondary or acquired one. Duke-Elder and Dobree[9] found only six reported cases. Amalric and Schum[10] recently reported a case and Chisholm and Dudgeon[11] did also, using fluorescein angiographic studies.

Patients previously described have been male, between the ages of 11 and 47; two exceptions were a 37-year-old woman described by Law[12] and a 36-year-old woman described by Hsin-Hsiang.[8] Our youngest patient was 4 years old and our oldest was 47 years of age. The differential diagnosis includes other rare retinochoroidal atrophic processes, such as helicoid peripapillary chorioretinal atrophy, proliferating choroiditis, angioid streaks of the retina, and other retinochoroidal disorders with peripapillary or radial atrophic lesions, or both.

The prognosis for vision in pigmented paravenous retinochoroidal atrophy is believed to be good with minimal field defects and rare impairment of central visual acuity. Contrary to this pattern, two of our patients (Cases 1 and 3) had widespread functional impairment of a progressive nature that may accompany this disorder and lead to serious visual disability.

Summary

Three male patients had paravenous pigmented retinochoroidal atrophy. Extensive retinal function tests showed characteristic retinal pigment epithelial abnormalities on fluorescein angiography, loss of peripheral visual field, diminution of the electroretinographic b-wave, and elevated rod threshold on dark adaptometry.

The disease appears to be more progressive than previously indicated, and in late stages, may cause legal blindness through involvement of the posterior pole. No treatment is known.

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OPHTHALMIC MINIATURE

I am journeying, say, in the west of England. I cross a bridge over a stream dividing Devon from Cornwall. These two counties, each beautiful in its way, are quite unlike in their beauty; yet nothing happened as I stepped across the brook, and for a mile or two or even ten I am aware of no change. Sooner or later that change will break upon the mind and I shall be startled, awaking suddenly to a land of altered features. But at what turn of the road this will happen, just how long the small multiplied impressions will take to break into surmise, into conviction—that nobody can tell.

Sir Arthur Quiller-Couch, *On the Art of Writing*
G. P. Putnam's Sons, 1916

SPECIFIC HISTOCOMPATIBILITY ANTIGENS ASSOCIATED WITH BEHÇET'S DISEASE

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Our previous reports[1,2] have shown that patients with Behçet's disease carry the antigen HL-A5 significantly more often than control subjects. In the present study, we investigated 15 patients from our first study, as well as a new, independent group of 29 patients, to test if we could confirm our previous findings.

SUBJECTS AND METHODS

Forty-four patients with Behçet's disease, 25 men and 19 women ranging in age from 19 to 59 years (Table 1), were typed for HL-A antigens. Fifteen patients included in a previous study were retyped with new antisera.

As to the classification of the patients,[3] 35 belonged to the complete type and nine to the incomplete type (Table 2). There were two patients with neuro-Behçet's disease. In contrast to the lengthy duration of the extraocular lesions, most patients suffered less than six years from ocular lesions (Table 3).

The permanent control panel consisted of 78 unrelated healthy adults; all were members of the Red Cross Blood Center.

We performed HL-A typing by using the lymphocytotoxicity test in plastic microtest trays and the two-stage procedure of Amos.[4]

More than 60 highly selected antisera were used to recognize HL-A1, HL-A2, HL-A3, HL-A9, HL-A10, and HL-A11 in the LA sublocus, and HL-A5, 4c, HL-A7, HL-A8, HL-A12, HL-A13, W10, and W27 in the FOUR sublocus. The designations of the antisera and their corresponding antigens are described elsewhere.[5] Determination of HL-A5 was based on reactions obtained with three reliable anti-HL-A5 sera: Byron

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TABLE 1

SEX AND AGE DISTRIBUTION OF THE PATIENTS WITH BEHÇET'S DISEASE

Age, yrs	Men	Women	Total
0–10	0	0	0
11–20	1	1	2
21–30	6	2	8
31–40	11	9	20
41–50	4	6	10
51–60	3	1	4
Total	25	19	44

TABLE 2

CLASSIFICATION OF THE PATIENTS WITH BEHÇET'S DISEASE

Type	No. of Patients (%)
Complete	35 (79.5)
Incomplete	9 (20.5)
Without ocular lesions	6
Without genital ulcers	3
Suspect	0 (0)
Possible	0 (0)
Total	44 (100)

TABLE 3

DURATION FROM THE ONSET OF OCULAR AND EXTRAOCULAR LESIONS

Duration, yrs	No. of Patients with	
	Ocular Lesions (%)	Extraocular Lesions (%)
0–3	24 (54.5)	9 (20.4)
4–6	14 (31.8)	12 (27.3)
7–9	2 (4.5)	11 (25.0)
10	4 (9.2)	12 (27.3)
Total	44 (100)	44 (100)

65-0-04-14-01, Cronin 5/28/71, and Schmidt 2-71-1-02-24-01. The 4c antigen determination was based on McMullen 65-0-03-30-01, Rafter 1027 F, and SA pool 1 (Ao).

We studied three families in which the patients were positive for HL-A5. Four patients and 11 healthy family members were typed for the determination of HL-A genotypes and haplotypes.

Results

The frequency of HL-A antigens in patients with Behçet's disease and in normal control subjects is shown in Table 4. Similar to our previous results, 75.0% of the patients manifested the HL-A5 antigen, a frequency significantly greater than the control subjects manifested ($\chi^2 = 22.1$, $P < .0001$). More 4c antigen (which consists of HL-A5, W5, and W18 in white subjects) was seen in the patients (90.9%) than in the control subjects (41.0%). The χ^2 test was significant ($\chi^2 = 26.9$, $P < .0001$).

In this study, the increase of HL-A2, observed among patients in our previous report, was insignificant. The increased incidence of HL-A10 among these patients also proved to be statistically insignificant. These deviations may be considered a chance effect.

As to W27,[6] we observed no patients with this antigen, as was the case with the control subjects. No significant differences were observed in the distribution of other HL-A antigens.

We compared the antigen frequencies of HL-A5, and 4c with reference to the complete and incomplete types (Tables 5 and 6). However, the differences were insignificant for both antigens.

Family 1—A 21-year-old man (Fig. 1)* had neuro-Behçet's disease.[7] His elder brother had inherited the haplotype (a) from his father and the haplotype (c) from his mother. The patient inherited the haplotype (b) and (d) from his father and mother, respectively; they showed a normal Mendelian pattern of inheritance of the HL-A antigens.

Family 2—A 45-year-old woman had the complete form of Behçet's disease (Fig. 2). She had inherited the haplotype (a) and

* The antigen SA 1 (Sapporo No. 1) in Family 1 and 2 (Figs. 1 and 2) denotes a possible new HL-A specificity associated with W22. This is an antigen that has not received an official designation from the International Committee on Nomenclature.

TABLE 4

Frequency of HL-A antigens in Behçet's disease*

HL-A Antigens	Subjects		
	Controls (%)	Behçet's Disease (%)	P†
1	0 (0)	1 (2.3)	N.S.
2	30 (38.5)	19 (43.2)	N.S.
3	3 (3.8)	0 (0)	N.S.
9	41 (52.6)	22 (50.0)	N.S.
10	16 (20.5)	15 (34.1)	.08<P<.12
11	11 (14.1)	6 (13.6)	N.S.
5	24 (30.8)	33 (75.0)	P<.0001
4c	32 (41.0)	40 (90.9)	P<.0001
7	8 (10.3)	3 (6.8)	N.S.
8	1 (1.3)	1 (2.3)	N.S.
12	7 (9.0)	1 (2.3)	N.S.
13	1 (1.3)	0 (0)	N.S.
W10	14 (17.9)	10 (22.7)	N.S.
W27	0 (0)	0 (0)	—

* 78 control subjects, 44 patients with Behçet's disease.
† N.S. indicates not significant.

TABLE 5

HL-A5 FREQUENCIES BETWEEN COMPLETE AND INCOMPLETE TYPES OF BEHÇET'S DISEASE*

	Complete Type	Incomplete Type	No. of Patients
HL-A5	27	6	33
Other antigens	8	3	11
Total no. of patients	35	9	44

* $X^2 = 0.047$; $.8 < P < .9$ (not significant).

TABLE 6

4c FREQUENCIES BETWEEN COMPLETE AND INCOMPLETE TYPES OF BEHÇET'S DISEASE*

	Complete Type	Incomplete Type	No. of Patients
4c	32	8	40
Other antigens	3	1	4
Total no. of patients	35	9	44

* $X^2 = 0.056$; $.8 < P < .9$ (not significant).

(d) from her parents. The HL-A genotype of her 30-year-old youngest brother was identical with her genotype. However, this brother had been in good health for 30 years, and had no sign of Behçet's disease.

Family 3—This family has a case of familial occurrence of this disease (Fig. 3). A 29-year-old woman, the eldest sister, manifested the complete form of Behçet's disease; she inherited the haplotype (a) and (c) from her parents. She was homozygous for HL-A5. Her younger brother, a 23-year-old patient with the complete form of Behçet's disease, had (b) and (c) haplotypes. Thus, the HL-A genotypes of two siblings in Family 3 with this disease were different, the opposite of the findings in Family 2.

DISCUSSION

The present study revealed that the antigen frequencies of HL-A5 were significantly increased in 29 patients with Behçet's disease, confirming our previous observations.

Among 29 patients from the new, independent group (Table 7), HL-A5 and 4c were significantly increased ($P < .0001$), and the distribution of other HL-A antigens was consistent with both the previous series and the total.

Antigen 4c, known for its close correlation with Hodgkin's disease,[8,9] occurs frequently in the Japanese population, although we know it consists of HL-A5, W5, and W18 in white subjects. In this study, 4c frequencies were also significantly higher in patients with Behçet's disease; however, it seems to represent the influence of narrow HL-A5. The frequencies of 4c*, the so-called W5-W18 complex in white subjects, are 15.9% in the patients and 10.3% in the control subjects, with no significant difference ($\chi^2 = 0.84$, $.3 < P < .4$).

At the Fifth International Workshop on histocompatibility testing, Mittal and associates[10] showed that of 129 Japanese individuals living in Los Angeles, none had

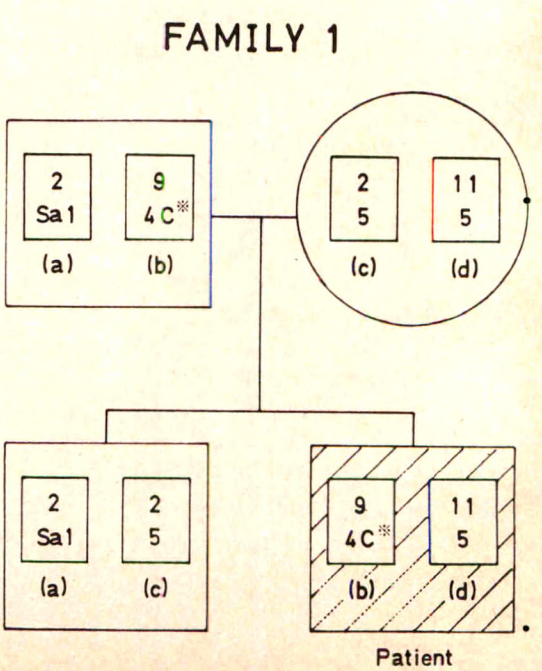


Fig. 1 (Ohno and associates). Results of HL-A genotypes in Family 1 where the patient has neuro-Behçet's disease. Squares designate males and circles designate females.

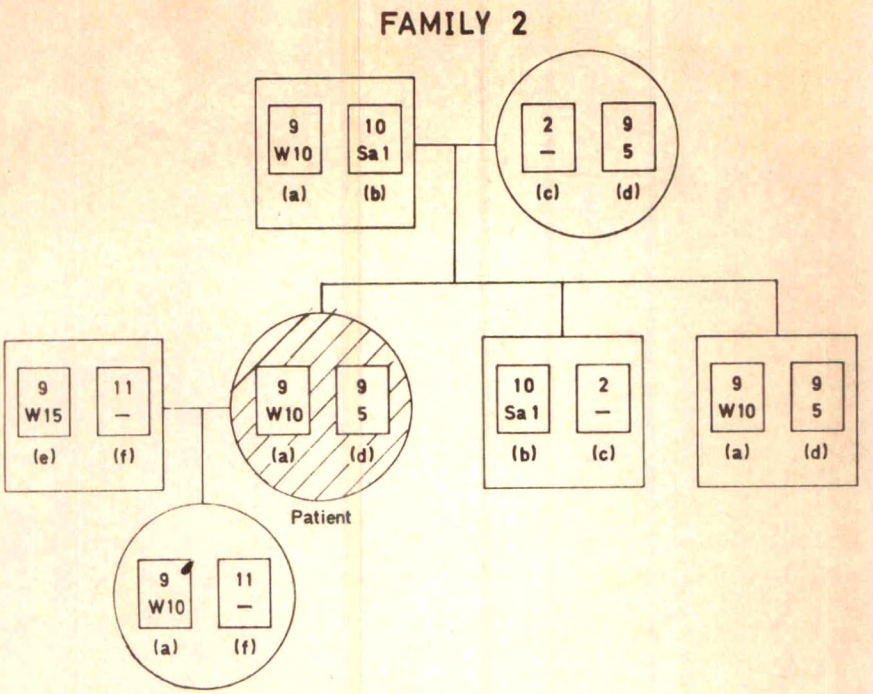


Fig. 2 (Ohno and associates). Results of HL-A genotypes in Family 2 where the patient has the complete type of Behçet's disease.

either W5 or W18. These authors stressed the heterogeneous nature of HL-A5 among the Japanese.

Since 4c*, which seems to be a new component or a variant of HL-A5 in the Japanese,[11] has not been directly associated with this disease, a similar significant association between classic HL-A5 and the patients with this disease probably could be found not only in Japan, but in the Mediterranean countries or elsewhere.

The mechanism of the association between HL-A5 and Behçet's disease is not known, but there have been possible explanations.[12,13] The first postulated mechanism of association is that HL-A5 may function as a specific receptor of pathogens. The second mechanism might be the phenomenon of "cross-tolerance," wherein the antigenic determinants of some exogenous pathogens could mimic HL-A5 antigens. The third and the most probable mechanism is concerned with the effects of immune-response

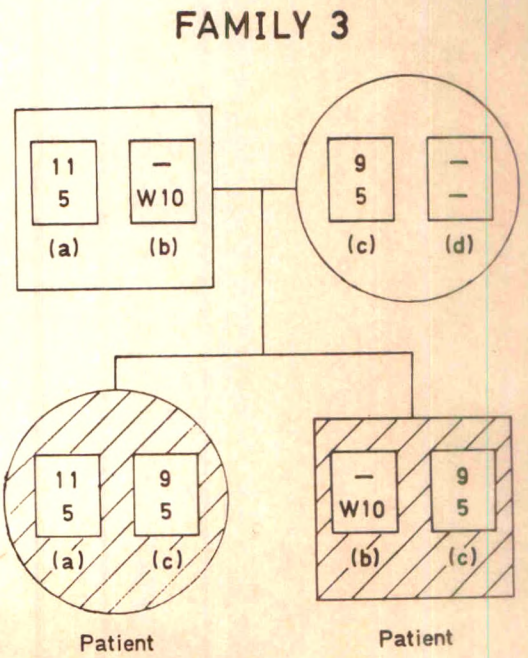


Fig. 3 (Ohno and associates). Results of HL-A genotypes in Family 3 which contains a case of familial occurrence of Behçet's disease.

TABLE 7

HL-A5 AND 4c FREQUENCIES IN TWO CONSECUTIVE SERIES OF BEHÇET'S DISEASE*

	Controls	Patients		
		First Series	Second Series	Total
Total no. of patients	78	15	29	44
HL-A5	30.8%	66.7%, .01 < P < .02	79.3% P < .0001	75.0% P < .0001
4c	41%	93.3% .0006 < P < .0007	89.7% P < .0001	90.9% P < .0001

* Values expressed in percent positive; probability.

genes linked to HL-A loci. In this case, there is relative linkage disequilibrium between HL-A and immune response loci. Recently, several specific immune-response genes influencing disease susceptibility were reported in man in the major histocompatibility region.[9,14,15]

These data of our three family studies may also suggest that genes controlling the susceptibility to Behçet's disease are not of the HL-A series itself, but of another series, such as the immune-response loci, mixed lymphocyte reaction loci, or disease susceptibility loci, closely linked to the HL-A region. The reason that HL-A5 is regarded as one of the most important genetic markers in the investigation of immunogenetic backgrounds in this disease is that some linkage disequilibrium may exist between genes controlling the susceptibility to this disease and HL-A5.

SUMMARY

We studied the distribution of HL-A antigens in 44 patients with Behçet's disease and in 78 normal control subjects. The antigen frequencies of HL-A5 and 4c were significantly increased in the patients (HL-A5: $\chi^2 = 22.1$, $P < 0001$; and 4c: $\chi^2 = 26.9$, $P < .0001$).

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Ophthalmic miniature

"Few books have more than a temporary life; like the daily newspaper, nine books in every 10 are read and thrown aside. (This leaves out of account the great mass of books that have no purpose and are never read.) Not one copy in a million is worn out by use, yet most books are printed and bound as though they were to be used forever. As a consequence few men can afford to buy many books, and those who do buy have to stand the excessive cost of small editions. We believe the successful book maker of the future will print for the million as well as for the few, and that good books, particularly scientific books, could be sold for a quarter the price now asked. Printed on thin yet clean white paper, the books could be sold, unbound, for the price of a magazine."

Scientific American
March 1875

ENDOTHELIAL SURVIVAL IN CORNEAL TISSUE STORED IN M-K MEDIUM

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To meet the increasing demand for donor corneal tissue, McCarey and Kaufman[1] developed a simple method of intermediate-term corneal preservation that extends the time donor corneas could be stored before transplantation. Several groups have reported successful series of transplants using corneas preserved in M-K medium,[2-4] and ultrastructural changes progress slowly in the endothelial cells of rabbit corneas stored up to 14 days in M-K medium.[5]

Preliminary electron microscopic studies of cat corneas stored in M-K medium or modified M-K medium in our laboratories confirmed the latter study. Trypan blue staining of the same corneas, however, indicated that after five days of storage, more than 30% of the endothelial cells were nonviable although most of the cells remained intact when examined by scanning electron microscopy. To resolve this discrepancy, cat corneas were stored at refrigerator temperature in either M-K medium or on the intact globe in a moist chamber, and the tissue was then incubated in fresh culture (TC-199) at 35°C for two hours before staining with trypan blue and fixation for electron microscopy. We thought those cells that were viable would resume their normal functions during the incubation, whereas nonviable cells would become disrupted. As expected, the percentage of disrupted cells present after incubation correlated with the percentage of cells that had stained with trypan blue in each cornea.

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Reprint requests to Diane L. Van Horn, Ph.D., Research Service/151, Veterans Administration Center, Wood, WI 53193.

MATERIAL AND METHODS

Cats were killed by an overdose of sodium pentobarbital and the eyes were immediately enucleated. We used cat rather than rabbit corneas in this study because (1) they can be removed from the globe with a 2-mm scleral rim more easily than rabbit corneas, and (2) they do not roll up during storage in M-K medium. In the preliminary series of experiments, the corneas were excised with a 2-mm scleral rim and one of each pair was placed in cold M-K medium (TC-199 and 5% dextran to which 125 units/ml of freshly thawed penicillin and streptomycin were added). The other cornea was placed in modified M-K medium (TC-199 and 1% chondroitin sulfate and antibiotics). Both corneas of each pair were stored for the same length of time (one to nine days) before removal and staining with 0.25% trypan blue, made in 0.9% saline for 1.5 minutes.[6] After staining, the corneas were carefully rinsed in saline and fixed in 2.67% glutaraldehyde. One person estimated percentages of stained cells in the fixed corneas. One half of each cornea was critical point dried from Freon 13 for scanning electron microscopy and pieces of the other half were flat embedded in a low viscosity epoxy resin for transmission electron microscopy.

In the second set of experiments, one cornea of each pair was stored in M-K medium and the other on the intact globe in a moist chamber. Both were refrigerated and stored for the same time period (one to seven days). After storage, both corneas of a pair were removed, placed in fresh TC-199, and incubated in sealed vials in an oven at 35°C for two hours. The corneas were then stained with trypan blue and prepared for electron microscopy as described.

Results

The results of trypan blue staining were similar in the preliminary studies (storage for one to nine days in M-K medium or modified M-K medium but no incubation at 35°C before staining) and in the studies in which the stored corneal tissue was incubated for two hours (Table). Less than 5% of the endothelial cells stained with trypan blue when the corneas were stored for one to four days and there was no difference between the corneas stored in M-K medium, modified M-K medium, or moist chambers. In contrast, after five to nine days, 20% or more of the cells stained in 17 of 21 corneas that had been stored in M-K medium.

In those corneas that were stained and fixed without incubation, scanning electron microscopy revealed that most of the cells were intact and the normal mosaic-like pattern of polygonal endothelial cells was maintained, even in corneas in which 50% or more of the cells had stained. Transmission electron microscopic examination of thin sections also confirmed that the cells had been structurally preserved with little change in the appearance of subcellular organelles, even after ten days of storage in either medium.

Conversely, in those corneas that were incubated at 35°C, the percentages of disrupted endothelial cells seen by scanning electron microscopy correlated with the percentages of cells that had stained with trypan blue. In one to four days, less than 5% of the cells were disrupted (Fig. 1, A and B) except for streaks of dead cells seen in some corneas after four days (Fig. 1, C and D). The streaks of cells also stained with trypan blue but were not included in the percentage estimate of stained cells. After five days, many cells were disrupted in both the M-K and moist chamber-stored corneas (Fig. 2) and the percentage of disrupted cells correlated with the percentage of cells that had stained with trypan blue in each cornea.

Transmission electron microscopy revealed that except for some cytoplasmic swelling, the subcellular organelles in the intact endothelial cells appeared normal (Figs. 3 and 4). The posterior plasma membrane was disrupted in the nonviable cells and cellular debris included swollen nuclei and mitochondria (Fig. 4).

TABLE

CHANGES IN ENDOTHELIAL VIABILITY IN CAT CORNEAS STORED IN MEDIA AT REFRIGERATOR TEMPERATURE*

Duration of Storage, days	Moist Chamber and 2-hr Incubation at 35°C	M-K Medium and 2-hr Incubation at 35°C	M-K Medium	Modified M-K Medium
1	0	0	0	0
	1+	0		
	1+	1+		
2			0	0
			0	0
3	0	0	0	0
	1+	1+	0	0
	1+	1+		
4	1+	0	1+	1+
	1+	0	1+	1+
5	0	1+	4+	4+
	1+	1+	4+	
	1+	2+	4+	
	3+	3+	4+	
	3+	4+		
		4+		
		4+		
		4+		
7	2+	2+	3+	2+
	4+	4+	4+	4+
			4+	
			4+	
9			3+	3+
			3+	3+
			4+	3+

* 0 indicates 1% or less of cells stained with trypan blue; 1+, 2–10%; 2+, 10–20%; 3+, 20–30%; 4+, more than 30%.

Discussion

In the preliminary studies, endothelial viability and ultrastructural integrity were compared in cat corneas stored in M-K medium and in TC-199 with chondroitin sulfate instead of dextran. The reason for making this comparison was that a clini-

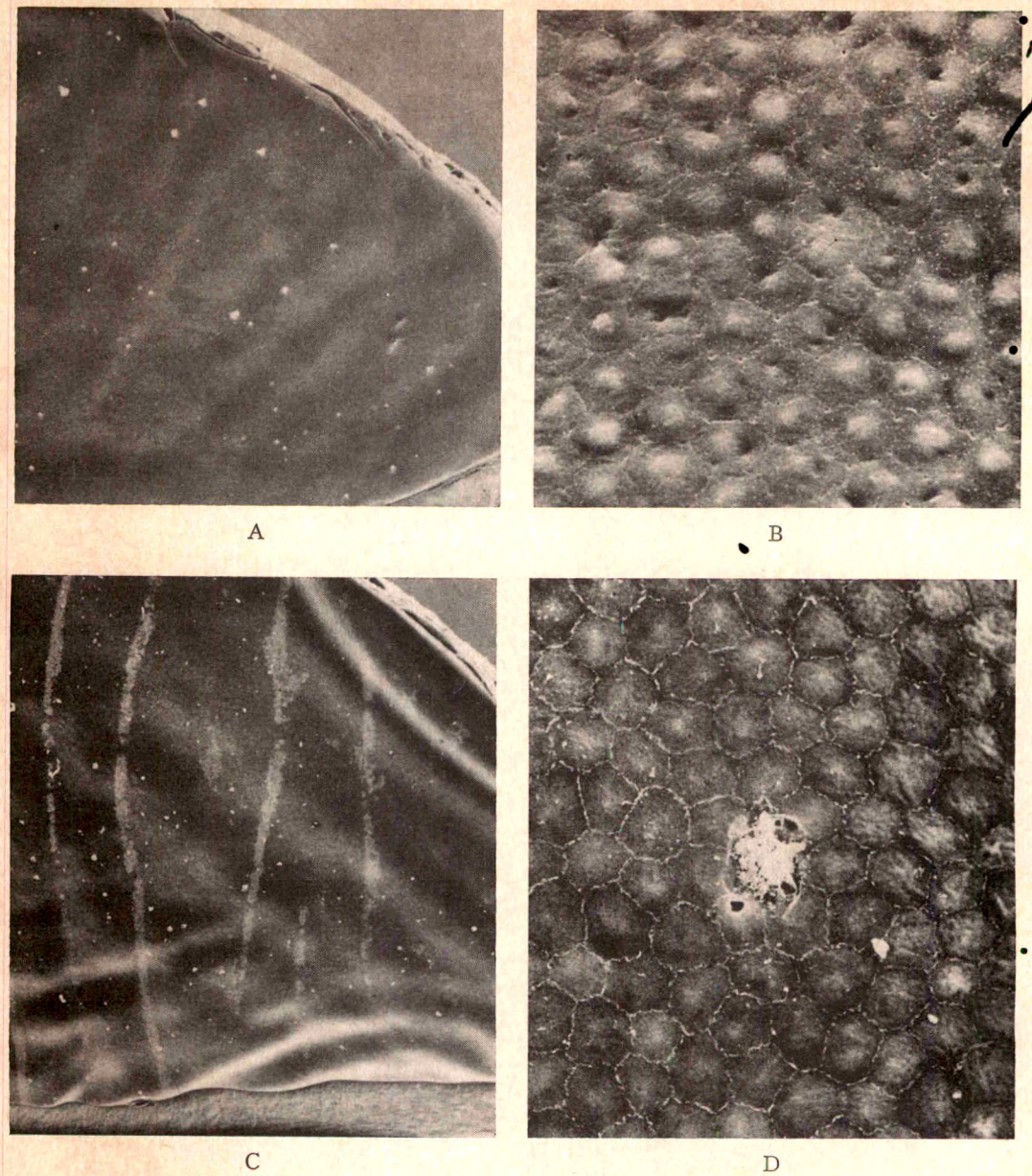


Fig. 1 (Van Horn, Schultz, and DeBruin). Scanning electron micrographs of the endothelium of cat corneas stored in refrigerated M-K medium for one day (A and B) and four days (C and D) before incubation in TC-199 for two hours at 35°C. A, Low-power micrograph of one fourth of a cornea showing that 99% of cells remained intact after one day (×20). B, High-power micrograph of same cornea showing normal mosaic-like pattern of polygonal cells (×500). C, Low-power micrograph showing streaks of dead cells present after four days (×20). D, Single dead cell surrounded by intact cells in same cornea (×500).

cally successful method of intermediate-term storage of donor corneas in a balanced salt solution containing 1% chondroitin sulfate had been reported.[7] There was no difference in our trypan blue staining or electron microscopic results between corneas stored in M-K medium or modified M-K medium, which suggests that chondroitin sulfate, a nor-

mal constituent of corneal stroma, may be substituted for dextran in M-K medium.

Our electron microscopic results on non-incubated tissue also confirmed the study of McCarey, Sakimoto, and Bigar[5] in which the endothelium of rabbit corneas was shown to be structurally preserved for at least nine days in M-K medium at refrigerator temperatures. We have also shown, however, that structural preservation does not necessarily reflect the ability of the cells to resume their normal function under more physiologic conditions. The incubation at 35°C in fresh TC-199 simulates the conditions to which donor corneas are exposed during and after transplantation surgery. When only a few endothelial cells die during storage of the donor tissue, the remaining cells probably are able to spread and re-establish an intact functional monolayer of cells after surgery. The exact percentage of donor cells that must be viable to maintain

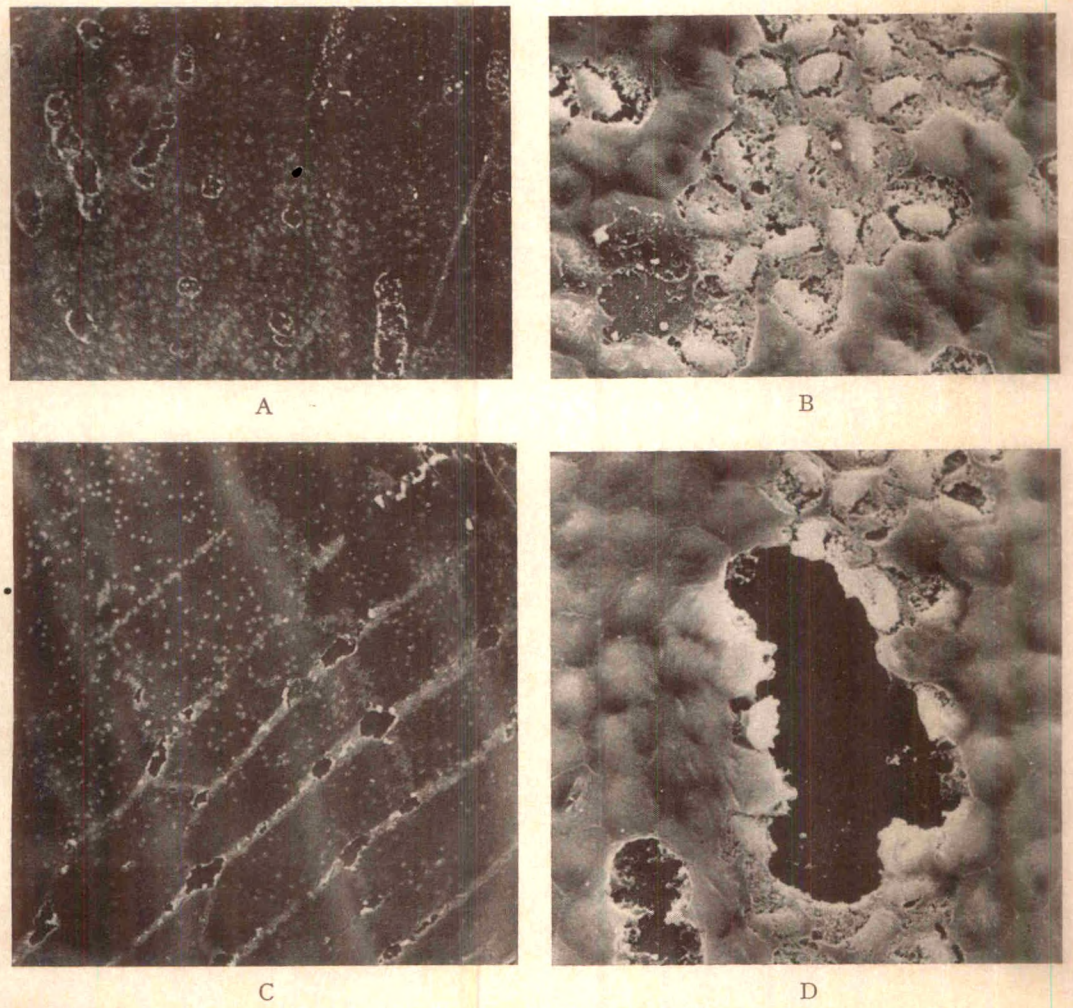


Fig. 2 (Van Horn, Schultz, and DeBruin). Scanning electron micrographs of cat corneas stored five days in refrigerated M-K medium (A and B) and five days in a refrigerated moist chamber (C and D) before incubation in TC-199 for two hours at 35°C. A, Low-power micrograph showing large percentage of disrupted cells after five days in M-K medium (×30). B, High-power micrograph of dead and intact cells in same cornea (×500). C, Low-power micrograph showing streaks and randomly scattered dead cells in moist chamber cornea (×20). D, High-power micrograph of a streak in same cornea showing loss of cells as well as disrupted cells (×500).

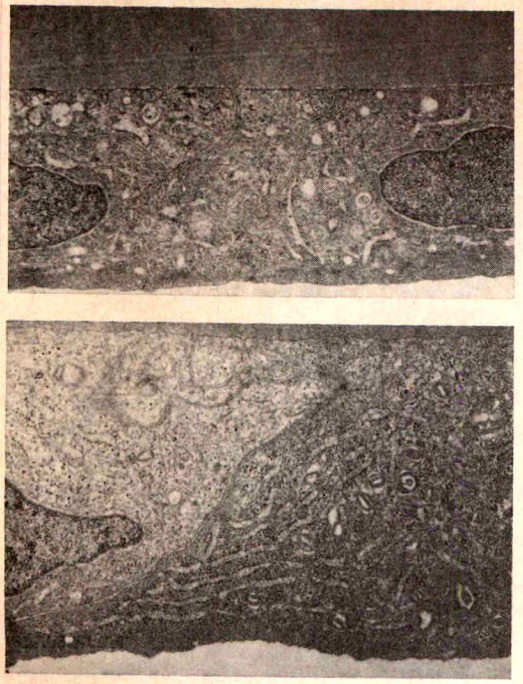


Fig. 3 (Van Horn, Schultz, and DeBruin). Transmission electron micrograph showing normal ultrastructure in intact endothelial cells (in same cat corneas as Figure 1). Top, M-K medium for one day (×9,000). Bottom, M-K medium for four days (×11,000).

transparency of the grafted button is not known.

Stocker[6] suggested that a donor cornea should be rejected for grafting if more than 30% of the cells stain with trypan blue. If we use this criterion, many of the cat corneas stored in M-K medium longer than four days probably would not be considered suitable for transplantation because 30% or more of the endothelial cells were no longer viable. Furthermore, the cat corneas used in this study were "ideal tissue" (that is, tissue from young animals placed in the medium immediately after death of the animal). Therefore, the time that human donor corneas can be successfully stored in M-K medium may be even less. In a series of 28 human transplants with donor tissue stored in M-K medium, four of the five buttons that resulted in cloudy grafts had been stored four days or longer.[2] This suggests that future clinical trials must be carefully designed and reported to determine if storage in M-K medium actually prolongs the time that human donor corneas can be stored before transplantation.

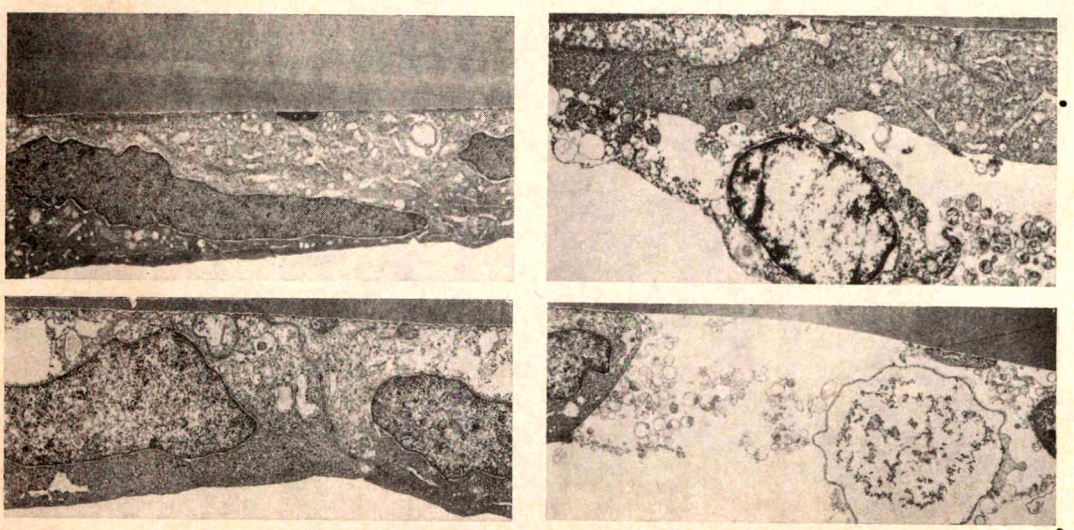


Fig. 4 (Van Horn, Schultz, and DeBruin). Transmission electron micrographs of intact and disrupted endothelial cells (in same corneas as Figure 2). Top, M-K medium for five days. Bottom, Moist chamber for five days. Some cytoplasmic swelling is present in intact cells, especially in the moist chamber-stored cornea (bottom left). The posterior plasma membrane is disrupted and mitochondria and nuclei are exposed in the dead cells (right) (×4,000).

Summary

Cat corneas were stored at refrigerator temperatures in M-K medium (TC-199, 5% dextran), modified M-K medium (TC-199, 1% chondroitin sulfate), or on the intact globe in moist chambers for intervals of one to nine days. Less than 5% of the endothelial cells stained with trypan blue in corneas stored one to four days, regardless of the method of storage. In contrast, after five days, 20% or more of the cells took up the stain in 17 of 21 corneas stored in M-K medium. Although stain uptake indicated nonviability of cells, most of the endothelial cells remained structurally intact when observed by scanning and transmission electron microscopy unless the corneas were incubated in fresh TC-199 for two hours at 35°C before trypan blue staining. In that case, the percentages of disrupted cells observed at each time interval correlated with the percentages of cells that had stained in each cornea. These results indicated that storage in M-K medium did not extend the time donor corneas can be stored before transplantation beyond four days.

Addendum—Since the submission of this paper, 23 human corneas have been treated in a similar fashion (incubation in fresh TC-199 at 35°C for two hours after storage in M-K medium for two to six days) with similar results. Less than 10% of the endothelial cells were nonviable (as assessed by trypan blue staining and scannning electron microscopy in one cornea stored two days, five corneas stored three days, five of six corneas stored four days, and three of nine corneas stored five days. Four of the latter nine corneas had 20 to 40% nonviable cells; two had 50 to 90% nonviable cells. An additional two corneas stored six days had more than 50% nonviable cells. More than 90% of the cells were nonviable in two corneas stored three days and two corneas stored five days on the intact globe in moist chambers.

Acknowledgment

The human donor corneas were supplied by the Wisconsin Lions Eye Banks in Milwaukee and Madison, and the Minnesota Lions Eye Bank.

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TRAUMATIC CENTRAL RETINAL ARTERY OCCLUSION WITH SICKLE CELL TRAIT

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The incidence of the sickle cell trait in the black population is 8.5%.[1] Such patients with ocular trauma should be carefully monitored for extended time periods as this hemoglobinopathy may increase the potential for vascular complications. Hemoglobin electrophoresis in black patients suffering ocular trauma could alert the physician to the need for more careful management and follow-up of the primary problem and such sequelae as glaucoma; additionally, knowledge of the presence of a hemoglobinopathy permits more judicious use of medications.

CASE REPORT

An 8-year-old black boy was in good health until he fell, striking his left brow and globe on the edge of a table. The patient had immediate blurring of vision, but because there was no significant pain, sought no medical attention. Over the next three to six days, pain in the left eye developed. On admission, he was unable to recall if the vision was worse than when the injury first occurred. The ocular examination revealed slight ecchymosis of the lateral left upper eyelid, 2+ bulbar conjunctival injection of the left eye, a hazy cornea, and a 5-ml, slightly deformed pupil nonreactive to direct or consensual light. Visual acuity was R.E.: 6/9 with pinhole, and L.E.: light perception with projection. Intraocular pressure in the left eye by applanation tonometry was 36 mm Hg with bedewing of the cornea, 2+ flare in the anterior chamber, and a hazy view of a large area of perimacular retinal edema. The right eye had unusual tortuosity of the vessels of the posterior pole (Fig. 1). Glycerin (Glyrol), oral acetazolamide (Diamox), topical corticosteroids, and cycloplegics were administered; the presumptive diagnosis was traumatic iritis with secondary glaucoma. Twenty-four hours later, applanation tensions were R.E.: 19 mm Hg, and L.E.: 34 mm Hg, with 3+ ciliary injection, 3+ flare and 3+ red blood cells (without hyphema level) in the anterior chamber. There was no evidence of a subluxated lens. The left optic disk was hyperemic with an excavated cup/disk ratio of 0.7 (Fig. 2), compared to the cup/disk ratio of 0.2 in the right eye (Fig. 1). Fluorescein angiography of the left eye demonstrated obstructed peripheral arterioles and leakage of dye from the disk with late staining (Figs. 3 and 4). Topical corticosteroids, acetazolamide, and glycerin were increased and one day later, intraocular pressure was R.E.: 12 mm Hg, and L.E.: 10 mm Hg. Visual acuity of the left eye was light projection despite the disappearance of corneal edema. With a decrease in intraocular pressure of 24 mm Hg in 24 hours, the disk had changed its appearance: from an excavated cup/disk ratio of 0.7, it was mildly elevated and hyperemic with a 0.2 cup/disk ratio. There was a nerve fiber layer infarct at the inferotemporal rim of the disk, markedly tortuous and full retinal veins, and a cherry red spot (Fig. 5). Angiograms of the left eye revealed blunting of the perimacular arterioles that ended in beads of fluorescence and nonfilling of the perimacular capillary bed (Fig. 6).

Since the clinical picture suggested a central retinal artery occlusion and possible ischemic infarction of the nerve head, whether due to vascular occlusion secondary to the posttraumatic increase in intraocular pressure or a shearing force at the lamina cribrosa at the time of injury that caused a papillitis, prednisone was administered orally to decrease swelling at the nerve head. Relative hypotony due to rapid lowering of the intraocular pressure may also have contributed to the change in the optic disk.

The following day, the red cell flare disappeared leaving only a thin inferior layer of blood in an otherwise normal-appearing angle. Intraocular pressure remained normal after discontinuation of glycerin and acetazolamide, and the patient was discharged on a regimen of cycloplegics, a topically applied corticosteroid, and a decreasing dose of orally administered corticosteroids. At this time, visual acuity in the left eye was light perception. The patient had sickle cell trait (HbA, 63%; HbS, 38%).

Two weeks after discharge, he showed a deafferented left pupil with an acuity of light perception, decreasing perimacular edema, increasing pallor of the optic disk, and a white sclerotic-appearing ghost vessel inferior to the macula. Four months later, the patient had no light perception in the left eye, an atrophic left disk, a left exotropia of 20 prism diopters, and intraocular pressure of 16 mm Hg, with absence of the previously noted inferior sclerotic arteriole, slightly attenuated but patent arterioles and venules, and a diffusely atrophic nerve fiber layer.

The x-ray films of the orbit and tomography of the left optic canal were normal eight months later.

From the Wills Eye Hospital, Philadelphia, Pennsylvania. This study was supported in part by National Eye Institute research grant EY00677-02.

Reprint requests to Richard E. Goldberg, M.D., Vascular Unit of the Retina Service, Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130.



Fig. 1 (Sorr and Goldberg). The normotensive right eye with increased vascular tortuosity and a cup/disk ratio of 0.1.

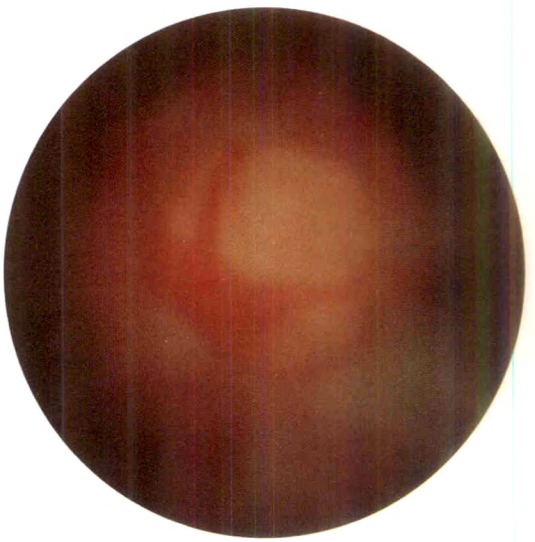


Fig. 2 (Sorr and Goldberg). The excavated disk of the left eye with an intraocular pressure of 36 mm Hg, and cup/disk ratio, 0.7. There is a nerve fiber infarct at the inferotemporal rim (compare with Figure 5).

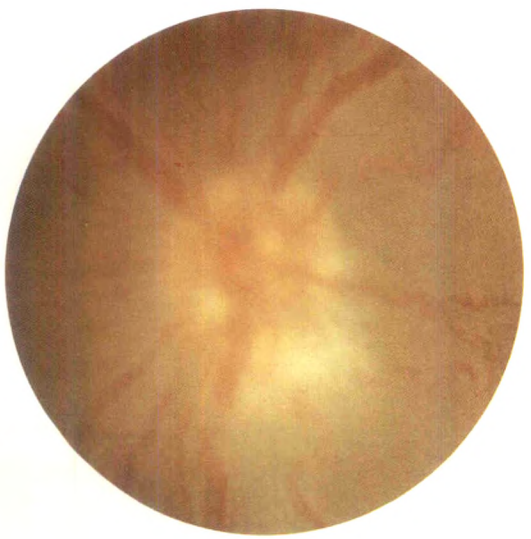


Fig. 5 (Sorr and Goldberg). The disk of the left eye, 24 hours later than in Figure 2, with an intraocular pressure of 10 mm Hg, showing hyperemia, and a nerve fiber infarct (compare with Figure 2).

Discussion

There are three nontraumatic cases of central retinal artery occlusion reported in association with electrophoretically proven sickle cell trait: a 36-year-old woman with systemic lupus erythematosus and tuberculosis who developed bilateral central retinal artery occlusions[2]; a 32-year-old man on active flying status with the Air Force[3]; and a 6-month-old infant with extreme dehydration, acidosis, pneumonia, and acute renal failure.[4] Michelson and Pfaffenback[5] reported two cases of central retinal artery occlusion in young patients with sickle cell trait following blunt trauma to the globe.

Our patient presented one week after the injury with a central retinal artery occlusion, traumatic iritis, hyphema, and moderately increased intraocular pressure with glaucomatous cupping of the disk. The modest increase of intraocular pressure to only 36 mm Hg ordinarily seems insufficient to explain the clinical picture and as the patient presented when he claimed to be most symptomatic, intraocular pressure may never have been significantly higher.

Leakage of fluorescein from the disk

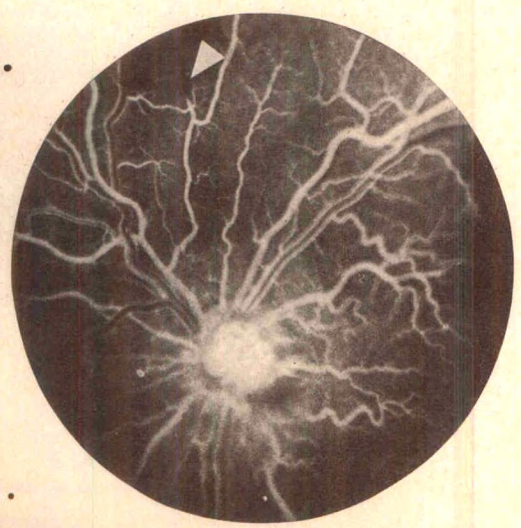


Fig. 3 (Sorr and Goldberg). Left eye showing arteriolar occlusion superiorly (arrow); intraocular pressure, 34 mm Hg.

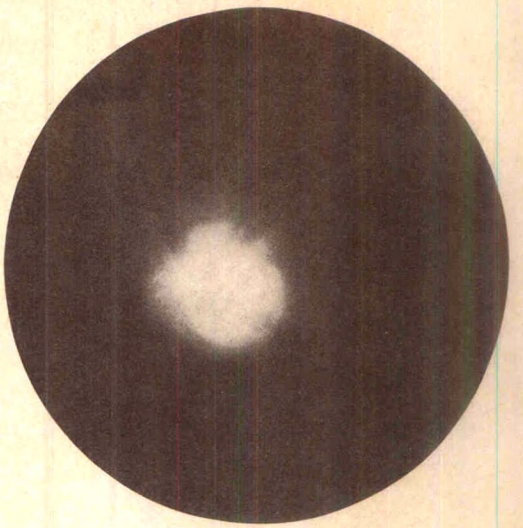


Fig. 4 (Sorr and Goldberg). Late fluorescein staining of the left optic disk; intraocular pressure, 34 mm Hg.

(Fig. 4) has not been described as a feature of central retinal artery occlusion.[6,7] Therefore, such leakage suggests optic nerve injury, as seen in angiograms of papillitis and optic nerve infarction.[8] Zimmerman[9] showed that severe acute glaucoma produces primary optic nerve injury characterized by papill-edema, axonal hydropic degeneration, and demyelinization. Fluorescein angiography performed in severe acute angle-closure glaucoma cases demonstrates leakage of dye from the disk.

A possible mechanism explaining the combined presentation of papillitis and central retinal artery occlusion in the present case is that ischemic optic neuropathy resulted from glaucoma and sickling, or from the injury caused by retrobulbar optic nerve contusion. In the latter instance edema thus produced would raise the optic nerve oncotic pressure, causing vascular compression, stasis, and hypoxia. Elevated intraocular pressure or a possible retrobulbar optic nerve contusion singly or in synergism may have induced sickling with resultant central artery occlusion and ischemic optic neuropathy.

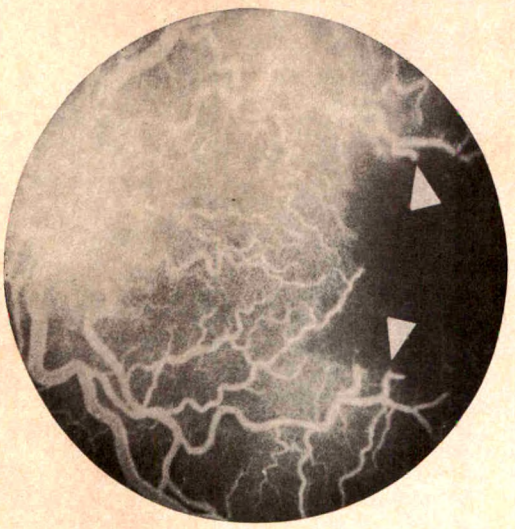


Fig. 6 (Sorr and Goldberg). Left eye demonstrating perimacular arteriolar blunting (arrows) and non-filling of the macular capillary bed; intraocular pressure, 10 mm Hg.

Summary

An 8-year-old black boy with sickle cell trait struck his left brow and globe on the edge of a table and had immediate blurring of vision. Six days later visual acuity was light projection, and traumatic iritis with secondary glaucoma and perimacular edema were present. Fluorescein angiography indicated obstructed peripheral and perimacular arterioles and dye leakage from the disk.

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THE HISTOPATHOLOGY OF PETERS' ANOMALY

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Peters' anomaly belongs to that group of congenital defects associated with the development of the anterior chamber. It is characterized by corneal opacity, anterior synechiae, and often, glaucoma.[1,2] Because of the sparse pathological material available for examination,[3-7] the pathogenesis of the glaucoma and corneal opacity is poorly understood. We report a case of Peters' anomaly, documented both by clinical examination and study of biopsy material.

CASE REPORT

A 23-month-old adopted boy of healthy Creole Indian parents was first referred to the Clinical Branch, National Eye Institute, in August 1972, with a diagnosis of bilateral congenital corneal opacities, more marked on the right eye than the left eye. The patient was the product of an 8½ month pregnancy and had a birth weight of 2,240 g. The mother and father were said to have had no hereditary disease.

Examination indicated normal dermatoglyphic pattern, no digital abnormalities, a head circumference in the 50th percentile, no hypertelorism, and an inner-outer canthus ratio of 0.35 (normal upper limit, 0.42). Results of systemic examination including the cardiovascular system were normal.

Under ketamine anesthesia, the horizontal and vertical corneal diameters were 11.2 × 11.0 mm in the right eye and 11.8 × 11.5 mm in the left eye.

Ultrasound measurements (A-scan) of the anteroposterior length in the right eye was 24 mm and 23.5 mm in the left eye. MacKay-Marg tonometry recorded an intraocular pressure in the right eye of 31 mm Hg, left eye 20 mm Hg; the intraocular pressure in the right eye was confirmed by direct manometry using cannulation of the anterior chamber and measured 32 mm Hg. Tonography indicated an outflow facility in the right eye of 0.10 µl/min/mm Hg with an intraocular pressure of 32 mm Hg, Schiøtz, and in the left eye of 0.25 µl/min/mm Hg with an intraocular pressure of 17 mm Hg, Schiøtz. On external examination of the right eye, there was a pale white vascularized and edematous area in the cornea in the lower nasal quadrant, extending from the corneoscleral limbus into the pupillary space and occupying the full thickness of the cornea (Fig. 1). The left eye had a much smaller and less dense corneal opacity that was not vascularized. On gonioscopic examination of the right eye, processes from the iris collarette extended across the anterior chamber to the corneal opacity. The angle was open 360 degrees but all angle structures were covered by heavy iris processes extending from the base of the iris onto the trabecular meshwork and onto Schwalbe's line. In the left eye, one iris process extended to the cornea at the site of the small opacity. The angle was open 360 degrees and ciliary body band, scleral spur, and trabecular meshwork were seen everywhere. There were few iris processes extending onto the trabecular meshwork and blood was seen in Schlemm's canal. On ophthalmologic examination of the right eye, the disk was elongated in the vertical meridian with slight cupping at the inferior pole. The cup/disk ratio was 0.6. In the left eye, the disk was round in appearance with a small cup, the cup/disk ratio being 0.1 to 0.2. The clinical impression was bilateral corneal opacities, more marked in the right eye and an angle abnormality in the right eye with a congenital glaucoma and early cupping of the optic nerve head. The possibility of initial microphthalmus of the right eye with secondary increase in size of the globe due to increased intraocular pressure was considered because of the relatively smaller cornea but slightly larger globe on the right as compared to the left eye. At the time of the first admission, a trabeculectomy with iridectomy was performed on the right eye without control of the intraocular pressure. A second trabeculectomy was performed one month later with scarring of the filtering bleb. At the time of this second operation, it appeared that the iris was ad-

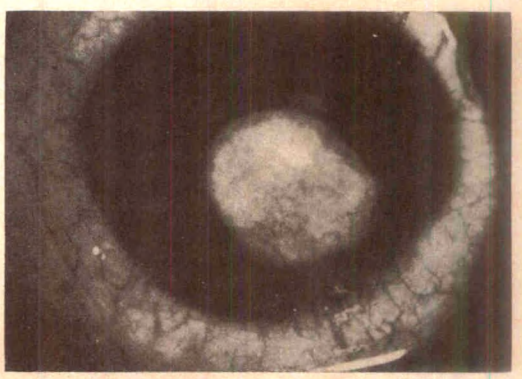


Fig. 1 (Kupfer, Kuwabara, and Stark). Right eye, vascularized and edematous corneal opacity.

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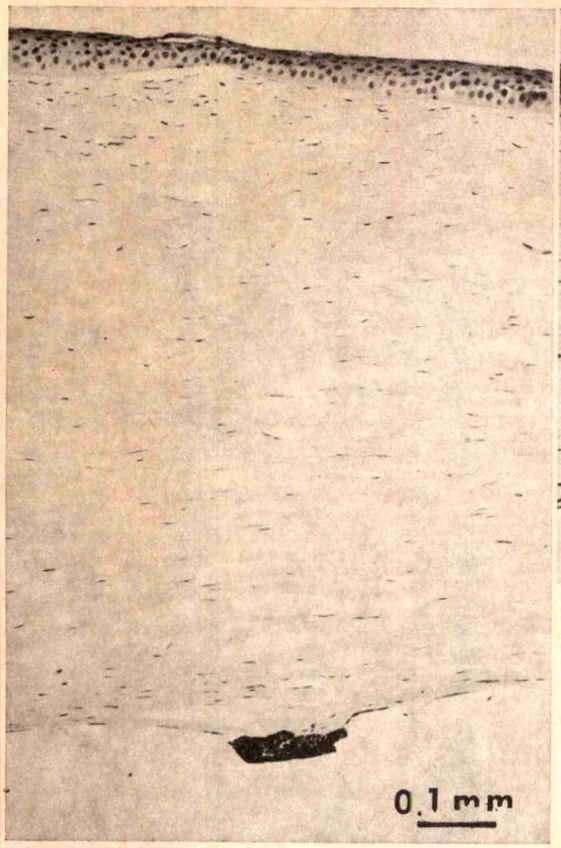


Fig. 2 (Kupfer, Kuwabara, and Stark). The area of the cornea to which iris tissue is adhering on the posterior surface is markedly edematous. Descemet's membrane is extremely thin (hematoxylin-eosin, ×100).

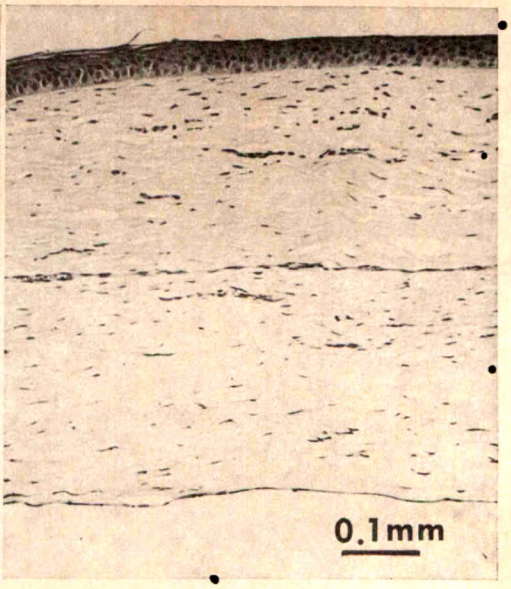


Fig. 3 (Kupfer, Kuwabara, and Stark). The scarred area of the corneal button. The stroma is highly cellular and vascularized. The posterior surface is covered with extremely thin endothelium (hematoxylin-eosin, ×100).

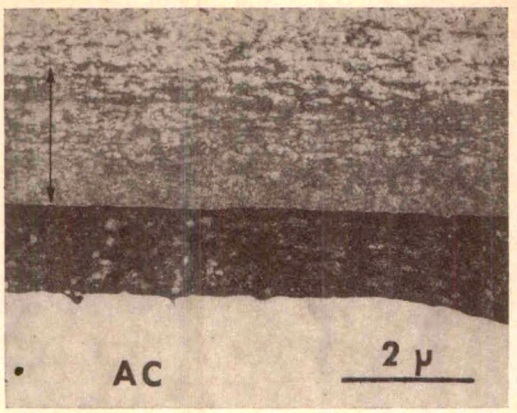
herent to the trabecular meshwork. Therefore, a cyclodiathermy of the right eye was performed after another month with adequate control of the intraocular pressure without medication. Accordingly, a 7-mm penetrating keratoplasty of the right eye was performed the following year.

Results

Histopathology—The excised tissues from the first trabeculectomy and the subsequent corneal transplant were fixed in 4% glutaraldehyde in 0.15M phosphate buffer (pH 7.2) for about 15 minutes at room temperature, and were cut into small pieces after proper orientation. The pieces were post-fixed in 1% osmium tetroxide in the same buffer solution, dehydrated in ethyl alcohol, and were embedded in an epoxy resin. Sections 1 μ thick were stained with toluidine blue for light microscopy. Ultrathin sections were stained with uranyl acetate and lead citrate and were examined by electron microscopy.

In some areas the iris from the first operation, as well as from the corneal transplant, adhered to the corneal endothelium or to trabecular meshwork. The corneal button was opaque in its entirety and in the area where iris tissue adhered, the stroma was markedly edematous (Fig. 2). The peripheral portion of the corneal specimen was vascularized and infiltrated (Fig. 3). The epithelium was irregular in its cellular arrangement and thickness, being detached from Bowman's membrane in several locations. The endothelium was not interrupted except at the area of the iris adhesion. However, the endothelial cells were extremely thin, measuring about 1 to 2 μ in thickness

(Fig. 4, top). The cells seemed to join tightly and contained normal micro-organelles. Electronlucent areas, compatible with clusters of glycogen particles, were present in the matrix (Fig. 4, bottom). Descemet's membrane was thin and its basal lamina substance was packed loosely (Figs. 4 and 5). Fine fibrils and collagen fibers were intermingled in the granular basal lamina substance. The appearance of Descemet's membrane was sim-



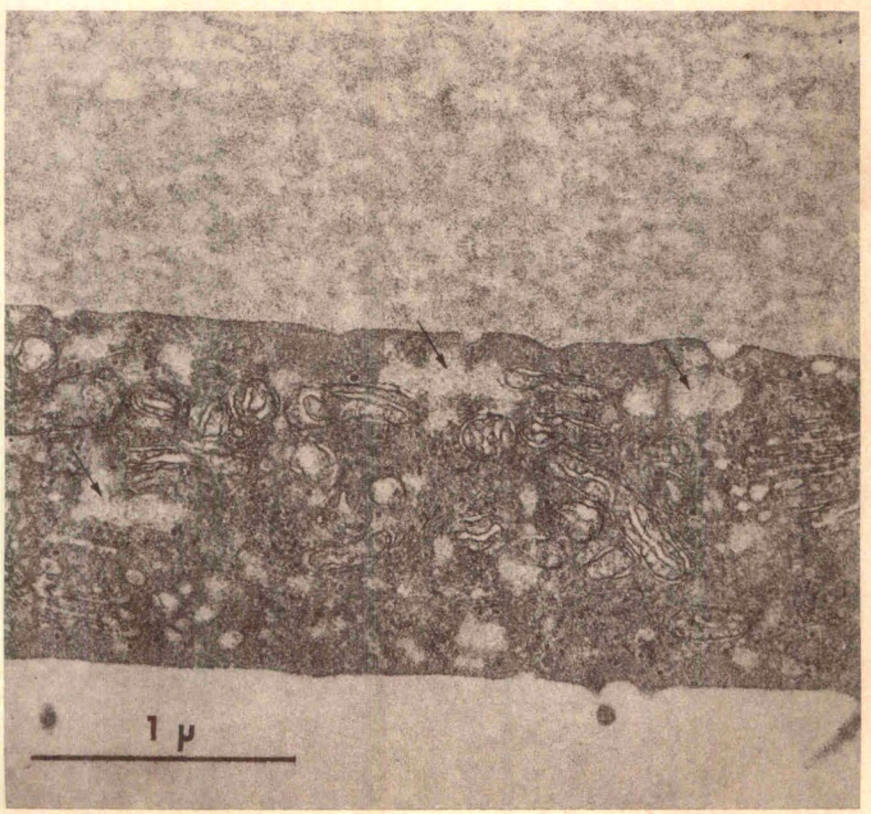


Fig. 4 (Kupfer, Kuwabara, and Stark). Top, The posterior portion of the cornea. The endothelium is thin. Poorly defined Descemet's membrane is indicated by arrows. AC indicates anterior chamber (×8,700). Bottom, The endothelial cytoplasm contains normal microorganelles. Clusters of glycogen particles are unusual (arrows). Descemet's membrane is loosely built (×34,500).

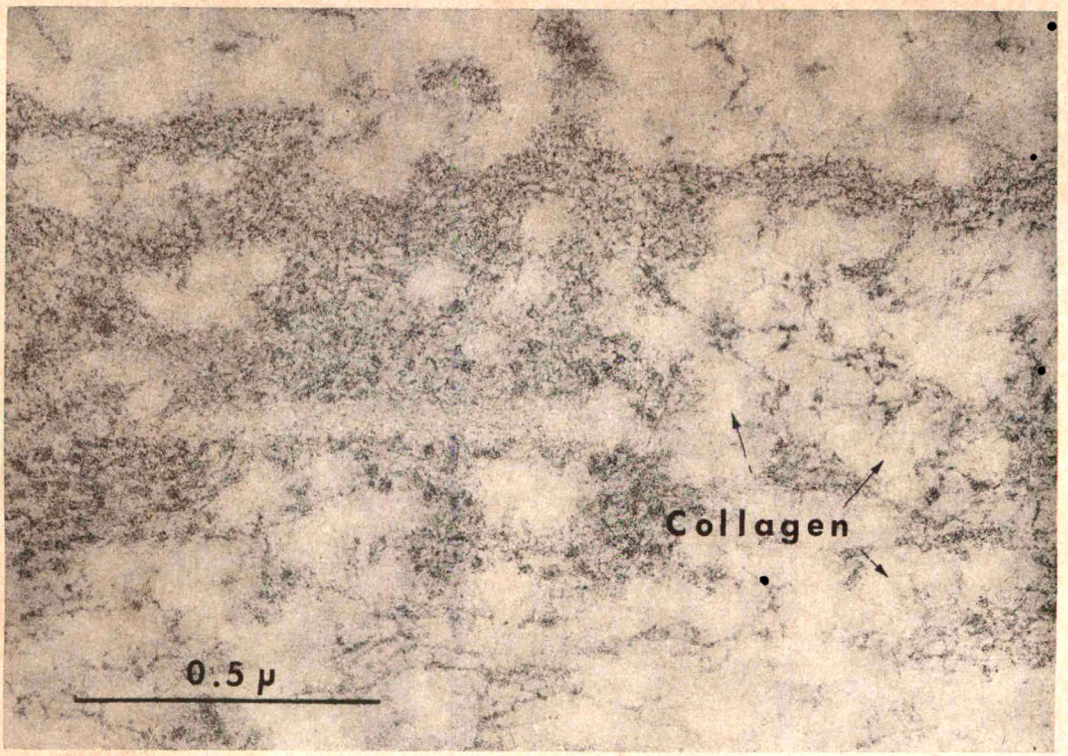


Fig. 5 (Kupfer, Kuwabara, and Stark). Descemet's membrane with abundant electronlucent collagen fibers and fine filaments (×80,000).

ilar to that seen in embryonal stages of development (Fig. 5). At the point where the iris tissue adhered to the loose connective tissue which had been formed posterior to Descemet's membrane, this connective tissue seemed to be continuous with that of the iris stroma (Fig. 6). In addition, pigmented iris cells formed a cluster at this point of adhesion. The posterior surface of the cornea adjacent to this point was covered with attenuated endothelial cells, while the iris tissue facing the anterior chamber was covered with pigmented iris epithelium. The original thin Descemet's membrane was present 3 to 5 μ anterior to the posterior surface. Also, a thin layer of abnormal Descemet's membrane was formed even more anterior to the original Descemet's membrane (Fig. 6). This pathological membrane was interrupted in several locations.

The specimen of trabecular meshwork and Schlemm's canal obtained at the time of the first operation demonstrated changes more commonly seen in old age. These consisted of the presence of abundant wide-banded collagen fibers with a periodicity of 100 mμ (Fig. 7). Additionally, the endothelial cells lining the trabecular beams contained phagocytosed pigment granules. By comparison, the region of Schlemm's canal demonstrated normal endothelial cells lining the canal (Fig. 8).

Discussion

From a review of the histopathology of eyes in which there was no keratolenticular contact or cataract, it has been concluded that the most characteristic corneal feature of Peters' anomaly is the abnormality of both the Descemet's membrane and the endothelium in the area of the corneal opacity and the thinning or absence of Bowman's membrane.[3-7] No electron microscopic examination of the region of the trabecular

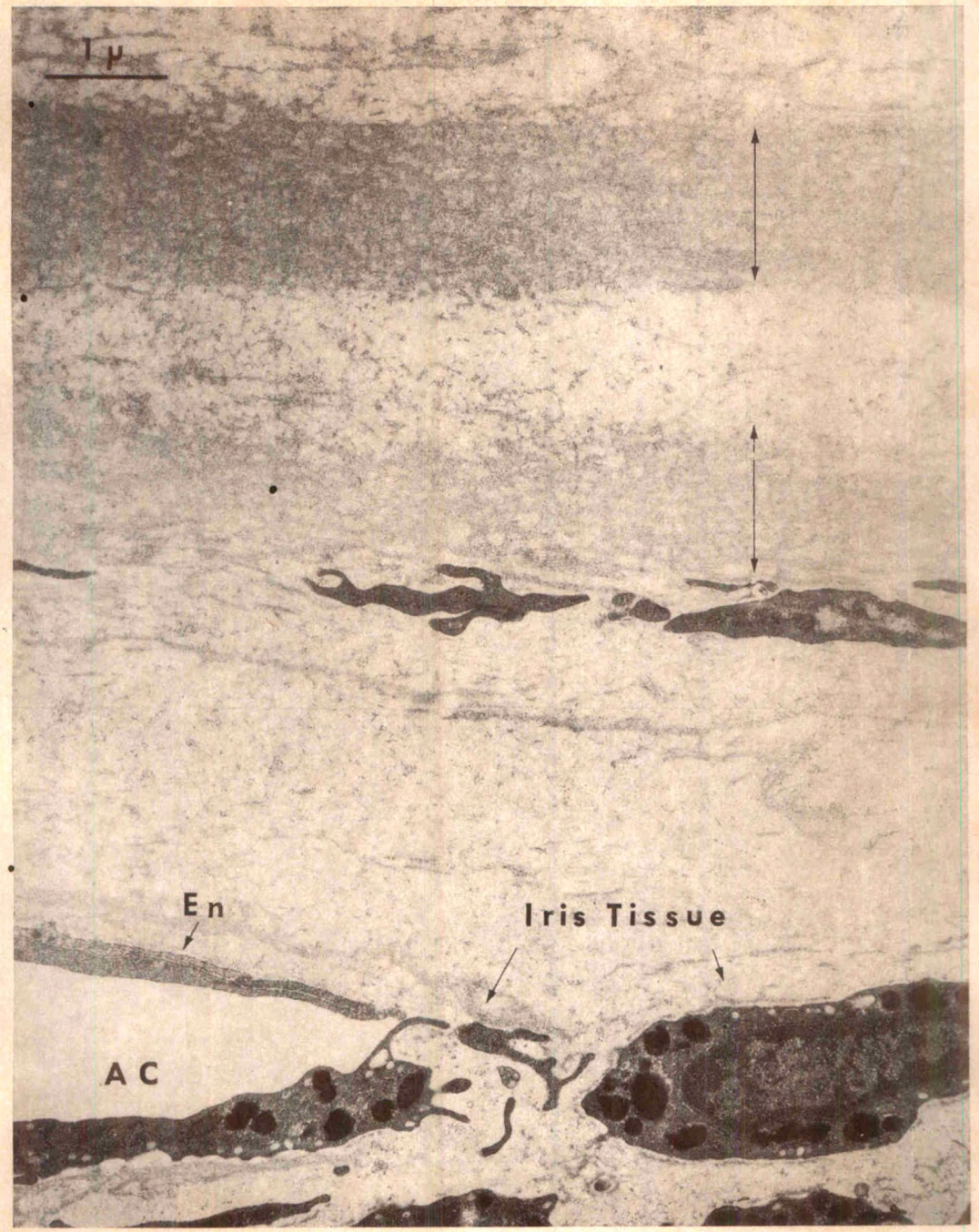


Fig. 6 (Kupfer, Kuwabara, and Stark). Area of the iridocorneal adhesion. The pigmented iris cells are surrounded by the basement membrane. Two layers of poorly defined Descemet's membranes are seen in the loose connective tissue (arrows). Extremely thin endothelial cells (En) are covering the posterior surface of the cornea. AC indicates anterior chamber (×17,000).

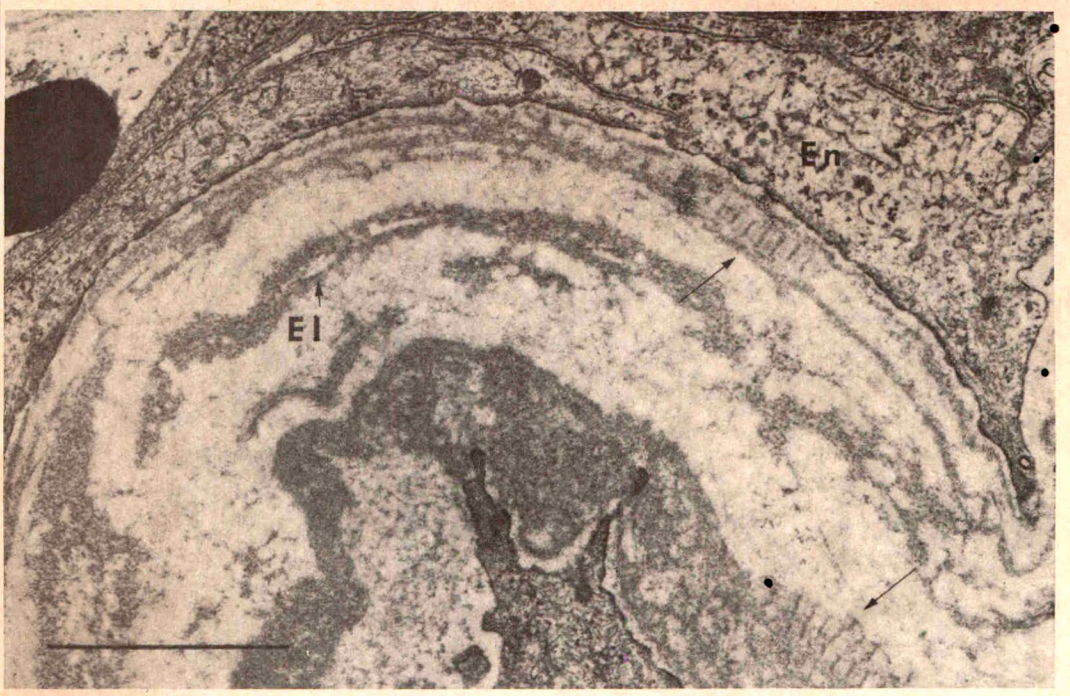


Fig. 7 (Kupfer, Kuwabara, and Stark). Trabecular meshwork showing the fine structure of the endothelial cells and a wide-banded collagen fibers (arrows). El indicates normal elastic fiber (×30,000). Bar gauge = 1.0 μ.

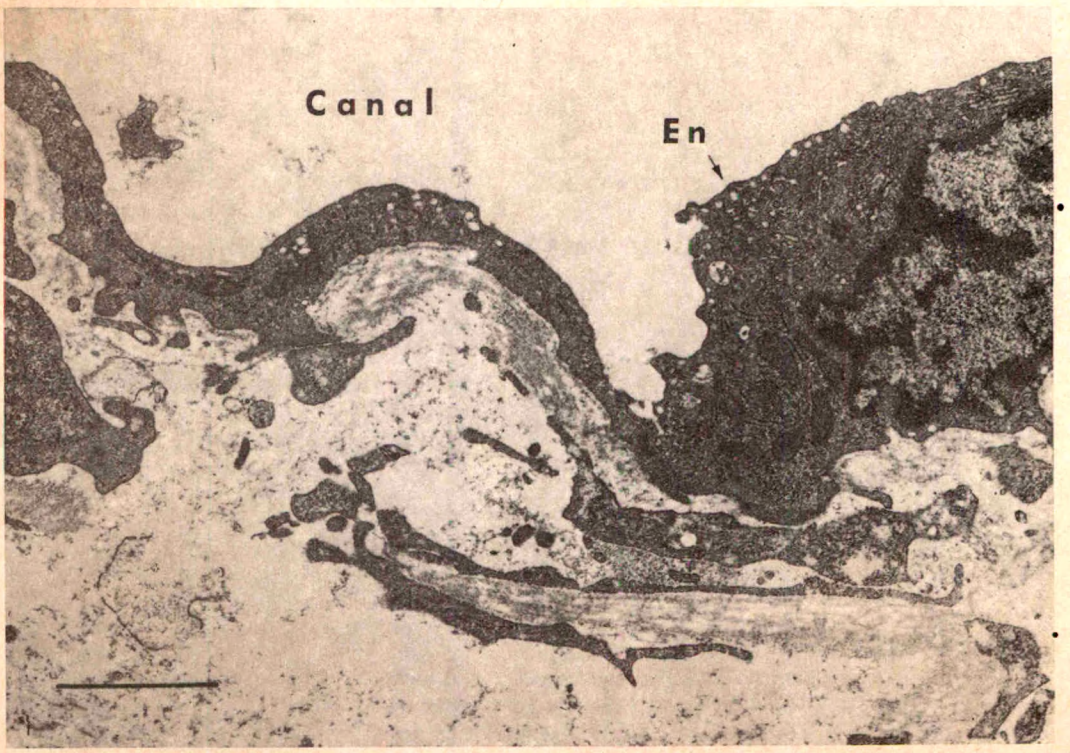


Fig. 8 (Kupfer, Kuwabara, and Stark). Endothelium (En) of the Schlemm's canal is normal (×20,000). Bar gauge = 1 μ.

meshwork and Schlemm's canal has been reported. In the present case, the corneal endothelial cells and Descemet's membrane although present in the region of the corneal opacity were abnormal in that the Descemet's membrane was immature in appearance and the endothelial cells were markedly attenuated. Only at the point of iris adhesion were Descemet's membrane and endothelial cells absent. The original Descemet's membrane was buried within the loose connective tissue in the posterior portion of the swollen cornea. Also, aberrant Descemet's membranes were found anterior to the original one. These findings suggest that the endothelial lining of the posterior surface of the cornea underwent loss in continuity on one or several occasions during the course of the pathological process. Although the denuded posterior surface at the site of the adhesion was covered with iris tissue, fluid from the anterior chamber may have penetrated into the cornea easily at this site through the loose connective tissue of the iris and entered the cornea, causing the edema.

Clinically, in the right eye, there were numerous iris processes adherent to trabecular meshwork. This eye had increased intraocular pressure and decreased outflow facility, suggesting that the abnormal morphologic changes of the endothelium covering the trabecular beams might have allowed for iris processes to become adherent to them. Other pathological changes included wide-banded collagen and phagocytosed pigment granules in the endothelial cells.

All these changes are customarily interpreted as senile changes and, for a 2-year-old child, represent an accelerated aging process. With the involvement of the endothelial cells of the cornea and trabecular meshwork, the basic abnormality appears to be a failure in the normal differentiation of the mesoderm of the rim at the optic cup into normal endothelial cells. However, an alternate hypothesis is attractive. Recent work[8] indicated that naturally labeled quail neural crest cells transplanted into the neural crest region of a stage-35 chick embryo become incorporated into corneal endothelium. Additionally, these quail neural crest cells also become incorporated into trabecular endothelial cells (according to a personal communication from M. C. Johnston and associates). In contrast the vascular endothelium, including the lining of the counterpart of Schlemm's canal in the chick, is formed from mesoderm. The neural crest origin of corneal and trabecular endothelial cells in the chick may also hold for other species including man. Thus Peters' anomaly may represent a failure of differentiation of neural crest cells destined for corneal and trabecular endothelium.

Why do the corneal endothelial cells appear to be secreting such a Descemet's membrane embryonal in nature? And why are the trabecular endothelial cells secreting membrane containing wide-banded collagen and showing other signs of aging? One possibility may be that the trabecular endothelium is more metabolically active than corneal endothelial cells with more active cell division as well as more rapid secretion of basement membrane. Thus, an abnormal corneal endothelium may secrete a sparse Descemet's membrane slowly while an abnormal trabecular endothelium may produce a rapidly aging membrane and shows evidence of early aging or other regressive changes.

Summary

Corneal, iris, and trabecular meshwork tissue in a 23-month-old boy with Peters' anomaly were studied with light and electron microscopy. In the cornea, both Descemet's membrane and endothelium were present beneath the area of the corneal opacity except at the point of iris adhesion. However, Descemet's membrane was thin and embryonal in nature, and the endothelium markedly attenuated. The trabecular meshwork demonstrated changes characteristic of old age such as wide-banded collagen and the presence of phagocytosed pigment granules in the endothelium. The iris appeared normal

except for anterior synechiae to the corneal opacity. Developmentally, the primary fault appeared to be a failure in the normal differentiation of endothelial cells of the cornea and trabecular meshwork.

ACKNOWLEDGMENT

Edwin Sheppard, M.D., referred this patient to the Clinical Branch, National Eye Institute.

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CLINICAL AND IMMUNOLOGIC RESPONSES IN PATIENTS WITH VIRAL KERATOCONJUNCTIVITIS

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Ocular viral infections manifest themselves in a variety of clinical pictures. Most commonly, the clinician finds follicular conjunctivitis, with or without accompanying keratitis. Epithelial and subepithelial corneal infiltrates are frequently observed with adenovirus infections, but also occur with herpes simplex and other viral-induced keratitis infections.[1,2] In addition to keratoconjunctivitis, viruses can (directly or indirectly) cause deep ocular involvement, including uveitis and optic nerve inflammation.[1]

In an effort to learn more about the etiologies of ocular viral infections and the pathogenesis of viral keratitis, we studied two groups of patients with epidemic and nonepidemic viral infections. All of them had follicular conjunctivitis, and many suffered from keratitis during at least one stage of their illness.

We had three major goals: to determine the rate of viral recovery from cases of nonepidemic acute or subacute follicular conjunctivitis; to compare the accuracy of clinical diagnoses with that achieved by culture or serologic studies, or both; and to explore the possible role of serum antibody in the formation and maintenance of corneal subepithelial infiltrates.

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We examined one group of patients who were involved in an epidemic caused by a single viral agent, and a second group of patients who were infected with many different viruses. Our results indicate that a variety of agents can cause similar illness patterns, and that clinical observation cannot always distinguish one from another.

Furthermore, serologic tests are a more accurate diagnostic method than clinical course in ocular viral illness, as is the case in systemic viral illnesses. Finally, viral antibody titers may correlate directly with specific clinical changes in adenovirus-induced keratoconjunctivitis.

MATERIAL AND METHODS

Patients—We studied two groups of patients by the following methods. The first was a population of 56 industrial employees who had epidemic keratoconjunctivitis. These patients were described in detail elsewhere,[3] but the data concerning their ocular findings were not presented.

The second group of 64 patients comprised a heterogeneous population seen during an 18-month period. The only criterion for selection was follicular conjunctivitis. All but nine patients were seen in the emergency room, clinic, or staff offices at Barnes Hospital from November 1971 to December 1972. The other nine were followed at the National Eye Institute from July 1970 to June 1971. One of us (H.L.S.K.) saw every patient during the acute or subacute phase of the illness and followed them until signs and symptoms abated. There were 32 males and 32 females, ranging in age from 3 to 77 years old (mean, 31.8 years). Twenty-nine

TABLE 1

ORGANISMS TESTED FOR IN THE SEROLOGIC STUDY

Influenza A, B, and C
Parainfluenza 1, 2, 3, 4A, and 4B
Newcastle disease virus
Mumps
Rubeola
Respiratory syncytial virus
Coronavirus OC-43, 229E
Vaccinia
Herpes
Varicella
Cytomegalovirus
Adenovirus types 1–33
Coxsackie A 7, 9, 16, and 21
Coxsackie B 1, 2, 3, 4, 5, and 6
Echovirus 4, 28
Acute hemorrhagic conjunctivitis
Mycoplasma pneumoniae
Bedsonia (TRIC)

patients were black, 33 were white, and two were orientals. All were ambulatory and in good health.

Collection of virus culture specimens—Fifty-eight of the 64 nonepidemic patients had viral cultures. A cotton swab was rolled in the inferior cul-de-sac and transferred to a carrier medium (sodium chloride, potassium chloride, dipotassium phosphate, charcoal, and agar, pH 7.0). The contents of this tube were either stored at −70°C for a short period or immediately transferred to tissue culture tubes of human diploid fibroblast, primary human embryo kidney cell, or human epidermoid carcinoma. Standard culture methods have been described previously.[4] All viruses isolated in this initial attempt were passed and compared to reference prototype virus strains for indication of atypicality.

The methods for viral culture in the 56 epidemic keratoconjunctivitis patients have been described elsewhere.[3] A single patient was cultured for trachoma inclusion conjunctivitis (TRIC) agent by other methods.[5]

Serologic studies—Of the original 64 study patients, 13 did not return for a convalescent serum. Therefore these serologic results are based on 51 patients. We collected sera during the acute phase and once or twice during the convalescent phase. There were two family groups in which a specimen from one uninfected member was considered acute and another infected member's specimen was considered convalescent. We took a convalescent specimen from 34 of the 51 patients within 30 days of the initial visit; 14 within 60 days; and three patients had specimens that were separated by more than 60 days.

The sera were tested for antibodies to the prototype strains of many respiratory and other viruses in order to survey all of the likely causes of follicular conjunctivitis (Table 1). Complement-fixation, hemagglutination-inhibition, indirect hemagglutination, or serum neutralization tests were employed as appropriate for each particular virus. The sera were heat-inactivated (56°C, 30 minutes) for all serologic tests. Antibodies to influenza A, B, and C, parainfluenza 1, 2, and 3, mumps virus "viral antigen," rubeola, respiratory syncytial virus (RS v), coronavirus OC-43 and 229E, herpes simplex 1, varicella, *Mycoplasma pneumoniae, Bedsonia* (TRIC agent), cytomegalovirus, and adenovirus group-specific hexon-antigen were assayed by the standardized complement-fixation test with overnight fixation of 5 units of complement.[4,6] Antibodies to influenza A and B, parainfluenza 1, 2, 3, 4A, and 4B, Newcastle disease virus, mumps virus, rubeola, coronavirus OC-43, vaccinia, and adenovirus types 1 to 33 were assayed by the standardized hemagglutination-inhibition test with 0.01M phosphate-buffered saline diluent and spectrophotometrically standardized 0.4% mammalian or 0.5% avian red blood cells.[7] Antibodies to coronavirus 229E were additionally measured by an indirect hemagglutination test.[8] Neutralizing antibodies to rubeola, RS v, selected adenoviruses, the six coxsackie B viruses, echovirus types 4 and 9, and coxsackievirus A-10 were assayed by serum neutralization tests in human epidermoid carcinoma or monkey kidney tissue culture.[9] Neutralizing

antibody titers to vaccinia, herpes, coxsackievirus A-9, A-16, and A-21, and four strains of acute hemorrhagic conjunctivitis virus were similarly assayed by serum neutralization tests in human diploid fibroblast tissue culture. Serum neutralization antibodies in coxsackievirus A-4 and A-7 were assayed in suckling mouse brain.[10]

For diagnostic purposes a fourfold titer change (either rise or fall) was considered significant for any of the serologic tests. In addition a stable titer of $\geq 1:32$ in any serologic test (hemagglutination-inhibition, serum neutralization, or complement-fixation) suggested infection with that agent if the clinical course and other serologic tests were confirmatory.

When serologic comparisons were carried out, as with the adenovirus groups described below, all of the testing was done in a standardized manner. We used only the hemagglutination-inhibition test, with 0.01M phosphate-buffered saline and standardized mammalian or avian red blood cells, to compare adenovirus types. Antigens for types 1 to 33 were maintained at the Center for Disease Control and were used for similar serologic studies in the past.[7] Other serologic test results did not enter into the calculations for significance of titer levels. We tested all sera simultaneously and in duplicate with the same cell lots whenever possible so that testing conditions and results would be equivalent.

Clinical examinations—Those patients who had epidemic keratoconjunctivitis[3] were examined during the initial phase of their illness and approximately one month after resolution of all symptoms. Visual acuity was recorded and, by slit-lamp microscopy, we made a determination of presence or absence of subepithelial infiltrates. There was no attempt to quantitate these or to judge severity.

The patients in the nonepidemic group were treated in a different manner. All patients were seen at least twice for evaluation of subjective and objective evidence of ocular illness. During each examination, we attempted to document severity of symptoms, visual acuity, the presence of pre-auricular nodes (or other adenopathy), and the appearance of the conjunctiva, cornea, and anterior chamber by slit-lamp microscopy. Detailed drawings of the cornea were made in keratitis cases, but the exact number of lesions was not recorded. Instead, we attempted to depict accurately the areas of cornea involved for future evaluation. Each patient was followed until keratitis showed signs of stability or actual regression. When possible, those patients with persistent lesions were followed for a longer time period.

At the end of the study period, all of the drawings were re-examined. For each patient we estimated the percentage of cornea involved with infiltrates during the acute phase of the illness. We assigned values before the serologic data were available. When all of the serologies were complete, the adenovirus groups were investigated separately. We calculated the severity of keratitis vs. serologic titer by hemagglutination-inhibition test values and the percentage of corneal involvement arrived at previously.

Therapeutic regimen—Almost all of the patients were treated with topical antibiotics, compresses, or astringents. Two of the patients in the adenovirus group received corticosteroids after cessation of the acute phase and when visual acuity decreased. Patients in the herpes group were given various antiviral preparations. Although these were generally effective in controlling the acute disease, we did not attempt statistical correlations to determine efficacy.

Ancillary studies—We took swabs for routine bacterial cultures in 26 nonepidemic patients simultaneously with the viral cultures. Although most of these were taken at random, occasionally patients presented with signs and symptoms suggestive of bacterial conjunctivitis complicating the viral illness; these patients were cultured specifically to identify possible infectious agents. In addition, conjunctival scrapings were examined

TABLE 2

RELATIONSHIP OF LENGTH OF ILLNESS TO VIRAL RECOVERY

	≤7 Previous Symptom Days	≥8 Previous Symptom Days
Adenovirus 3	2/4*	0/1
Adenovirus 7	3/6	0/6
Adenovirus 8	7/9	1/4
Herpes simplex	2/6	0/3
Herpes zoster	1/1†	0/2
Other‡	0/10	0/6
Total	15/36§	1/22

* Number of positive isolates per number of patients cultured.

† Skin lesion was positive, eye culture negative.

‡ Includes individuals who had cultures but no serologic studies; an additional patient (not included) had an isolate of adenovirus type 16, but she was unsure of the duration of her illness.

§ $\chi^2 = 9.5$; $P < .005$.

in 27 patients. These were processed with Giemsa or Gram stains, or both.

Tear studies—Tears were collected from ten patients with acute and chronic, nonepidemic viral infections or chronic noninfectious conjunctivitis. The details for collecting, processing, and quantitating immunoglobulins in tears have been described previously.[11,12] The viral serologic studies on the tear specimens were similar to those done on the sera from these individuals, but the tear specimens were not heat-inactivated and were diluted starting at 1:2 instead of 1:8. (Other studies involving the epidemic keratoconjunctivitis group have been described previously.[3])

RESULTS

Viral studies (nonepidemic patients)—Although more than 90% of the infected eyes were cultured, the yield of positive viral cultures was low. Table 2* shows the difference between the number of positive isolates obtained by culturing before or after the eighth day of illness. Culturable virus tended to disappear after the first week of illness in most of the virus groups examined.

Adenovirus isolates (types 3, 7a, 8, and 16) were typical prototype-like strains but three of the adenovirus type 7a viruses were not; these were neutralized or inhibited less well with prototype reference antisera than with the patient's own convalescent serum.[13] This was not clinically significant.

Serologic studies (nonepidemic patients)—Since positive viral cultures were sparse, the restrospective study of acute and convalescent sera constituted the major means of diagnosis. If cultures were positive or if clinical evidence pointed to a specific diagnosis—the presence of herpetic dendrites—the total battery of serologic tests (Table 1) was not always carried out.

We compared the clinical and serologic diagnoses in the 51 patients whose sera we examined (Table 3). All patients with positive cultures showed the expected serologic changes. Two patients appeared to have experienced infections with two agents, either simultaneously or in close temporal proximity. In one patient, the hemagglutination-inhibition titer to adenovirus type 7 was stable at 1:128, indicating a recent infection; at the same time, the culture for TRIC agent was positive.[5] The second patient had an illness characterized by initial upper respiratory infection and secondary chronic uniocular keratitis, with corneal ulceration and recurrences. Over the three months of observation during the chronic phase, he developed a gradual fourfold rise in adenovirus type 7 hemagglutination-inhibition antibody (1:32 to 1:128). Almost eight months after his initial illness he demonstrated signs of anterior uveitis after an upper respiratory illness (nonspecific) and increased his herpes simplex antibody titer fourfold (1:32 to 1:128) in both complement-fixation and serum neutralization tests. These data support a premise of double infections in both patients.

Five additional patients demonstrated sero-

* All of the data for the epidemic keratoconjunctivitis group were published elsewhere, except for the corneal quantitative material in clinical studies.[3]

logic changes suggestive of either sequential or simultaneous infection with two or three agents. However, in these patients we could not differentiate clinically among the various agents. Therefore, the serology that best fitted the clinical picture and time sequence of infection was chosen as the final diagnosis.

Most of the clinical misdiagnoses were made in the cases of presumed epidemic keratoconjunctivitis. Adenovirus type 7 was the most prominent masquerader, and herpes simplex passed for epidemic keratoconjunctivitis in one case.

We listed the geometric mean titers for the major adenovirus groups encountered in this study in Table 4. Although the average fold-rise in geometric mean titers was similar, the final absolute titers were different by more than twofold. This difference was statistically significant.

In an attempt to explain the higher final titer of the Group 1 adenovirus-infected patients, we looked at two different factors. The first was a consideration of a possible difference in the acute and convalescent phase serum samples (Table 5). The two groups were similar in makeup in that nine of 16 Group 1 patients and ten of 13 Group 2 were examined during the acute phase of their illness; they showed a fourfold rise in their titer to the infecting adenovirus.

There was a moderate disparity between patient history and the serologic data. Three Group 1 patients (Cases 8, 9, and 10) claimed they were ill for a few days, but their titer reflected a long-term illness ($\geq$ 32 initial or no change with time, or both). We observed one patient (Case 8) with an unchanging 1:16 titer throughout his illness and we could not explain the lack of change in titer. This disparity was less evident in Group 2 (Case 26).

The difference in acute phase geometric titer for each group was nearly signific-

TABLE 3

CLINICAL DIAGNOSIS COMPARED TO SEROLOGIC OR CULTURE-PROVEN DIAGNOSIS OF VIRAL INFECTIONS

Culture or Serologic Diagnosis	Clinical Diagnosis					
	Epidemic Kerato-conjunctivitis	Pharyngo-conjunctival Fever	Epidemic Kerato-conjunctivitis or Pharyngoconjunctival Fever	Herpes Simplex	Herpes Zoster	Follicular Conjunctivitis
Adenovirus Group 1						
Type 3	1	2	1	0	0	1
Type 7	4*	4	2	2	0	3†
Type 16	0	0	1	0	0	0
Group 2						
Type 8	12	0	1	0	0	0
Type 9	0	0	0	0	0	1
Type 29	1	0	0	0	0	0
Group 3						
Type 1	0	0	0	0	0	1
Herpes virus‡	2*	0	0	6	4	3
TRIC agent	0	0	0	0	0	1†
Total	20	6	5	8	4	10

* One patient who had serologic evidence of infection with both herpes simplex virus and adenovirus 7 is included twice.

† One patient who had serologic evidence of infection with adenovirus 7 and a simultaneously positive culture for TRIC agent is included twice.[5]

‡ Herpes group includes herpes simplex, varicella zoster, and cytomegalovirus.

TABLE 4

SEROLOGIC DATA FROM GROUP* AND TYPES OF ADENOVIRUSES

Adenovirus Type	GMT†	GMT of Sera With ≥Fourfold Changes	
		Acute	Convalescent
	Group 1		
3	73.5		
7	93.4		
3, 7, 16	84.5‡	9.3	86.3§
	Group 2		
8	41.5		
8, 9, 29	41.8‡	5.6	42.2§

* Grouping based on agglutination studies.[4,13]

† Geometric mean titer of total group (compare with Table 5).

‡ $t = 2.87$; $P < .01$.

§ $t = 2.64$; df, 17; $P < .02$.

by t-test (t) (Group 1 = 21.6, Group 2 = 8.9; $t = 2.00$, 27 degrees of freedom [df]; $.05 < P < .06$). However, when we considered only patients proven to be in the acute phase, the difference was not significant (5.6 vs. 9.3; $P > .1$).

There was a difference in the number of days between acute and convalescent samples for the two groups. Overall, the mean number of days was 21 for Group 1 and 29 for Group 2 (not significant). However, if only the 19 patients in the acute phase were again considered, the averages were 19 days and 32 days, respectively ($P < .05$; $t = 2.34$; df, 17). (From these data, a higher titer should have been expected for Group 2 because of the longer interval between acute phase and serum peak.) Thus, neither the titer of acute phase sera nor the sampling time of convalescent phase sera seemed to account for the difference in final antibody levels.

We also considered the degree of upper respiratory or generalized illness among patients in both groups. Of the 21 patients with serologic evidence of Group 1 infection, only 16 gave accurate histories; nine of these reported an associated upper respiratory infection with conjunctivitis. In contrast, one (with adenovirus type 9) of the 13 patients in Group 2 exhibited signs or symptoms of upper respiratory infection. This difference was again significant ($P < .01$, χ^2 test).

Thus, those with Group 1 nonepidemic adenovirus infection were afflicted with more upper respiratory infections, but these in-

TABLE 5

SEROLOGIC TITER CHANGES DURING ACUTE AND CONVALESCENT STAGES OF NONEPIDEMIC ADENOVIRUS KERATOCONJUNCTIVITIS

Case No.	Acute Phase Titer*	Convalescent Phase Titer*	Days Ill on First Visit	No. of Days Between Acute and Convalescent Sera
		Group 1		
1	4	128	≤7	22
2	4	128	≤7	30
3	4	32	≤7	12
4	4	128	≤7	11
5	8	64	≤7	13
6	32	128	≤7	40
7	32	128	≤7	18
8	16	16	≤7	28
9	64	64	≤7	14
10	128	128	≤7	14
11	8	32	≥14	15
12	32	128	≥14	18
13	32	64	≥14	50
14	64	128	≥14	25
15	256	256	≥14	12
16	64	64	≥14	15
		Group 2		
17	8	32	≤7	30
18	4	32	≤7	50
19	4	32	≤7	11
20	4	16	≤7	35
21	8	32	≤7	21
22	4	32	≤7	28
23	4	128	≤7	21
24	8	64	≤7	45
25	16	64	≤7	50
26	32	32	≤7	32
27	4	64	11	32
28	64	64	≥14	14
29	32	32	≥14	14

* Represents reciprocal of highest endpoint dilution in hemagglutination-inhibition test.

fections were not necessarily responsible for the significantly higher serologic titers. In fact, there was no significant relationship between the presence of an upper respiratory infection and a serologic response that equaled or exceeded 1:128 (Table 6). This negative correlation held true for changes in both homologous and heterologous virus titers. Therefore, the explanation for the higher serum titers in patients with Group 1 infections may not be related directly to the concomitant upper respiratory infections.

We compared the sensitivity of the two most commonly employed serologic tests (Table 7). Hemagglutination-inhibition tests demonstrated fourfold rises in many cases where complement-fixation tests failed to show significant changes. Hence, primary dependence on the usual complement-fixation hexon-antigen test would have resulted in fewer positive diagnoses, even in acute infections.

Ancillary laboratory studies (nonepidemic patients)—We microscopically examined conjunctival smears from 21 patients, and routine bacterial cultures were taken from 11 of these patients plus ten other individuals. Cultures from five patients showed coagulase-positive staphylococci; these patients had various diagnoses: adenovirus type 8 epidemic keratoconjunctivitis, adenovirus type 7 pharyngoconjunctival fever, herpes simplex keratitis, and a case of chronic "factitious" conjunctivitis.

The smears were helpful only in cases of herpetic infections. In three patients with herpes simplex and one with herpes zoster, the smears showed inclusion bodies or giant cells, or both. The histology of the other 17 slides was either nonspecific or not diagnostic of viral infection. Few had the typical predominance of mononuclear cell types, and most were composed of a mixed white blood cell population and epithelial cells.[14]

TABLE 6

THE RELATIONSHIP OF GROUP 1 ADENOVIRUS-INDUCED UPPER RESPIRATORY ILLNESS (URI) TO THE MAXIMUM SERUM TITER TO THE HOMOLOGOUS ADENOVIRUS

	Total	No. With Titer ≥1:128	Significance
Patients with URI	9	4	$\chi^2=2.7$
Patients without URI	7	5	$P>.1$

TABLE 7

COMPARISON OF THE MICROTITER HEMAGGLUTINATION-INHIBITION TEST (HI) TO COMPLEMENT-FIXATION TEST (CF) FOR DIAGNOSTIC CAPABILITY

Fold-Increase CF Titers	Fold-Increase HI Titer*		
	0–2	4	≥8
0–2	8	11	5
≥4	0	0	6

* $\chi^2=12.9$; $P<.0005$.

Clinical studies—EPIDEMIC KERATOCONJUNCTIVITIS—We observed 56 patients until their clinical symptoms abated and examined them with a slit lamp.[3] Twenty-eight patients showed signs of keratitis during their illness and had chronic subepithelial infiltrates when examined one month after resolution of the illness (16 of these experienced some degree of decreased visual acuity as well). The 28 remaining patients, who were also infected during the first wave of the epidemic were seen at the same time and had no subepithelial infiltrates. The peak geometric mean hemagglutination-inhibition titer of the former group with residual infiltrates was 1:31.5 (range 1:10 to 1:160). The data for the unaffected group were 1:102.5 geometric mean titer (range 1:20 to 1:320). This difference was significant ($P \leq .001$). (The collection of sera and intervals between examinations were similar for patients because they were part of an epidemic group.[3] The serologic tests were exactly the same as those carried out in the nonepidemic group, and often were done simultaneously).[4,6–8]

NONEPIDEMIC ADENOVIRUS INFECTIONS—Only the patients with Groups 1 and 2 adenovirus infections formed populations of sufficient size and homogeneity for statistical

TABLE 8

CORNEAL INFILTRATES AND ANTIBODY TITERS IN NONEPIDEMIC ADENOVIRUS-INFECTED PATIENTS

Case No.	Adeno-virus Type	Peak Titer*		No. of Eyes	Corneal Involvement		Residual Lesions	Decreased Visual Acuity
		Homologous	Heterologous		Present on 1st Visit	Maximum Involvement† (%) (Worst Eye)		
				Group 1				
1	3	128	<4	0	0	0	0	0
2	3	128	<4	2	+	20	0	+
3	7	32	<4	2	0	30	+	0
4	3	128	<4	0	0	0	0	0
5	3	64	5.3	0	0	0	0	0
6	7	128	<4	1	+	20	+	0
7	7	128	6.1	1	+	25	+	0
8	7	16‡	<4	0	0	0	0	0
9	7	64‡	<4	2	0	20	+	0
10	7	128	6.9	1	+	10	0	0
11	3	32	<4	1	+	50	+	+
12	7	128	<4	1	+	30	+	+
13	7	64‡	6.1	1	+	30	0	+
14	7	128‡	4.6	0	0	0	0	0
15	7	256‡	4.6	1	+	20	+	0
16	7	64‡	5.3	2	+	75	+	0
				Group 2				
17	9	32	4.2	0	0	0	0	0
18	8	32	4.0	2	+	25	+	+
19	8	32	5.7	2	+	50	+	+
20	8	16	4.0	1	+	35	+	0
21	8	32	11.3	2	0	40	+	0
22	8	32	7.1	2	+	75	+	+
23	8	128	5.7	1	+	100	+	+
24	8	64	8.6	2	+	25	0	+
25	8	64	7.1	2	0	30	+	0
26	8	32‡	5.9	1	+	10	0	0
27	29	64	13.7	2	+	75	+	0
28	8	64‡	4.8	2	+	40	+	0
29	8	32‡	4.0	2	+	40	+	0

* Represents reciprocal of highest observed dilution of antiviral activity to infecting (homologous) virus and the average reciprocal activity against other viruses in that group[4] (heterologous).

† Estimated maximum percent of cornea with epithelial or subepithelial infiltrates.

‡ Titers did not change significantly (≥fourfold) during the observation period (compare with Table 5)

analysis of corneal disease. Group 1 was composed of five patients with adenovirus type 3 and 11 patients with adenovirus type 7 infections. Group 2 contained 11 patients with adenovirus type 8 and one each with adenovirus type 9 and adenovirus 29.

The data concerning the corneal involvement and antibody levels of both groups were compiled (Table 8, compare with Table 5). Analysis by χ^2 testing showed several significant correlations. First, the number of eyes involved with corneal changes differed significantly in the two groups. In Group 1, there were five patients with no involvement, seven with one eye, and four with both eyes affected. Group 2 had only one patient without corneal changes, three patients with a single eye involved, and nine patients with both eyes involved ($\chi^2 = 5.94$; df, 2; $P \approx .05$). When this same factor

(number of eyes) was used, and the antibody levels were compared for all adenovirus infections (Groups 1 and 2), a more significant difference was noted. At a level of 1:64, there were 12 doubly involved patients, four with one eye, and three with no corneal involvement. At a level of 1:128, only one patient showed infiltrates in both eyes, six had single eye involvement, and three had no ocular involvement. The difference between the number of patients in these three categories proved to be statistically significant ($\chi^2 = 7.65$; df, 2; $P < .025$).

Correlations of the degree of corneal involvement with antibody level were also carried out. There was no difference between the two groups in the number of patients with central lesions vs. peripheral lesions of the cornea. This was reflected in the patients with decreased visual acuity (Table 8).

We devised a comparison of the two groups in terms of fold-rise in antibody titer (Figure). (The fold-rise was a reflection of the rate of antibody production as well as the amount of antibody.) As evidenced by the graph, the responses of the two groups were almost diametrically opposed. For each fold-rise in titer, the Group 1 patients had progressively less corneal involvement. For the same change in titer, the Group 2 patients showed progressively more corneal infiltration. However, the final level of antibody achieved was lower in Group 2 (compare with Table 4).

A similar difference in the two groups was noted at the 40% level of corneal infiltration. Only two patients (of 16) in Group 1 had infiltrates that involved $\geq 40\%$ of the corneal surface area. In Group 2, six of 13 patients were affected in the same way ($\chi^2 = 5.73$; df, 1; $P < .025$).

Finally, age was not a factor differentiating the two groups. The average age of Group 1 patients was 29.9 years; Group 2 patients averaged 30.5 years. The difference was not statistically significant ($t = .128$; df, 25).

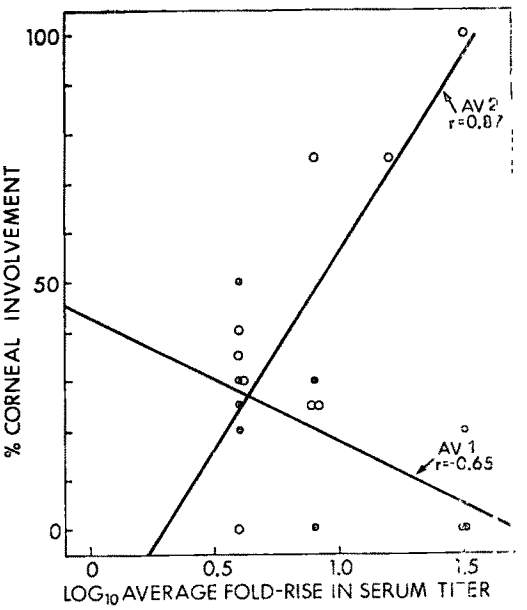


Figure (Knopf and Hierholzer). A comparis. of the percent corneal involvement with fold-rise i antibody titer among patients infected with Gro 1 (AV 1) and 2 (AV 2) adenoviruses. r repres t the correlation coefficient of the least-squares l calculated to fit the data. Only patients with at le a fourfold rise are included.

HETEROLOGOUS ANTIBODY RISES WITH ADENOVIRUS INFECTIONS (NONEPIDEMIC GROUP)—Rises in titers to heterologous vi ruses were observed in Groups 1 and 2 infe tions. Thus, in patients infected with adeno virus type 7 (Group 1), a significant chang in titer to this agent occurred, as well a smaller changes to such related types as 3, 11, and 21 (Table 8). However, rises in heterologous titers were more consistently seen in patients with Group 2 infections. For example, adenovirus type 8 infections produced rises to 12 related viral types in the Group 2 series. This was reflected in the higher heterologous average titers (Table 8). In particular, we noted a tendency for heterologous responders within family groups. In one of these families, all of the blood relatives showed changes in titer to several other Group 2 subtypes after adenovirus type 8 infection. However, the spouse of one member, exposed to the same virus, had a serologic change to adenovirus type 8 alone (homologous responder).

We observed patients with keratoconjunctivitis from other causes during this study (Table 3), but only adenovirus patients formed homogenous groups that lent themselves to statistical analysis. The herpes group was large (eight herpes simplex, two herpes zoster, two possible mixed herpes simplex-zoster, and three presumed cytomegalovirus), but heterogenous in terms of acute and chronic illness, treatment with various antiviral drugs or corticosteroids, and poor serologic responses. Variability in history, follow-up, and other factors occurred among the patients with adenovirus so the number of patients who met the criteria for various analyses often differed from one test to another. In terms of treatment, however, almost all of the patients with adenovirus required only therapy with topical vasoconstrictors or antibiotics, or both. Only two patients (one each from Groups 1 and 2) required corticosteroids for symptomatic relief, and this was instituted after achieving maximum corneal scores.

Analysis of tears—Ocular external secretions (tears) were analyzed in ten patients. In general, there were low antibody titers. Four patients with serologic diagnoses of herpetic infection represented chronic, recurrent keratoconjunctivitis or kerato-uveitis. Only one patient with disciform keratitis and uveitis had detectable tear-borne neutralizing antibody to herpes simplex. His serum titer, however, was not greater than 1:8 in a simultaneous neutralization test. One other patient showed tear antibody to herpes zoster and serologic changes consistent with simplex. Whether this represented true simultaneous infection or the presence of cross reaction was not determined.

Two patients had high titers (1:8, 1:16) to coronavirus OC-43 in their external secretions. Upper respiratory infection has produced antibody in tears[11] and this may represent that kind of relationship.

The predominant immunoglobulin species in the tears was IgA, in agreement with previous work.[11,12] However, we made no attempt to prove that the measurable hemagglutination-inhibition or serum neutralization antibodies were unique to IgA.

Discussion

Because all patients in the second part of this study were seen during a nonepidemic time period, the cases of keratitis were varied in their etiologies (Table 3). This observation agrees with previous studies that described a similar variety of viral agents responsible for epidemic keratoconjunctivitis keratitis.[15-18]

The behavior of the individual viral infections also conformed to expected patterns. Thus, Group 1 adenoviruses caused more upper respiratory and generalized illness, but less keratitis, than Group 2 infections.[1,2,19-21] Herpes viruses caused more severe keratitis and kerato-uveitis, but clinical illnesses correlated poorly with serologic changes in antibody titer.[22,23] We also encountered difficulty in culturing any virus after seven to ten days of symptoms. This has been reported before for epidemic keratoconjunctivitis, but it is probably true for many other viral syndromes.[2,24-26] We, like others, also found the hemagglutination-inhibition test to be superior to complement-fixation as a serum diagnostic procedure in adenovirus infection.[16] No procedure gave consistent results with tears.

There were differences in the extent of corneal involvement observed in Group 1 and 2 infections. The correlations indicate that Group 2 viruses produced a lower level of specific antibody titer (despite a longer time interval between the collection of acute and convalescent sera), and induced more corneal disease in the affected individuals.

These data suggest that the higher antibody titer in Group 1 protected the cornea, supported by examination of the keratoconjunctivitis epidemic of adenovirus type 8, a Group 2 virus. In the latter patients, a range of antibody was observed that was somewhat higher than that of the nonepidemic Group

1. (The reason for this difference is not readily apparent, but does not lie in testing differences, since both sets of sera were examined under identical conditions and often simultaneously.) What is more important, however, is the range of corneal involvement with this single viral agent. Once again, the patients with higher antibody titer experienced less corneal involvement with this usually virulent agent.[17,19]

The corneal infiltrates may only represent a pattern of infection and the antibody response to it. Certainly more than one viral type can cause this pattern, as shown in the nonepidemic group. Also, the same virus can cause different degrees of involvement (epidemic study), perhaps depending on the level of antibody illicited by the infection.

Since delayed hypersensitivity was not specifically assayed, the elevated humoral antibody in epidemic Group 2 or nonepidemic Group 1 patients may reflect a higher degree of overall immunity, and cellular immunity may be the chief deterrent of corneal disease. However, systemic antibody alone may protect the cornea (and even the fellow eye) from severe involvement. Whether it was humoral or cellular, or both, the nonepidemic and epidemic groups of patients displayed a reasonably similar pattern of protection that correlated with high antibody titer.

We only speculate about the pathogenesis of the subepithelial infiltrates. In studies of immune-complex disease, for instance, rheumatoid arthritis and Aleutian mink disease, antigen-antibody complexes in blood vessel walls can attract complement and inflammatory cells that cause the damage.[27,28] These complexes are made to persist by maintaining a low titer antibody, and the disease may be completely eliminated by raising the titer.[28] The cornea is similar to the collagenous tissue in the walls of blood vessels,[29] and these tissues can absorb certain antigens.[30,31] Therefore, it seems feasible that viral particles might be bound to the stromal collagen, form complexes with low levels of antibody diffusing within the cornea, and thereby act as a nidus for inflammation. The subsequent fixation of complement and attraction of inflammatory cells completes the subepithelial infiltrate seen by slit-lamp microscopy. Corticosteroids would disrupt the inflammatory response, but it would not remove the complexes. Hence, discontinuation of the drug would allow inflammatory cells to reappear.[32] A similar set of circumstances was proposed in the pathogenesis of stromal disease in herpes simplex keratitis.[33]

Based on these suppositions, one may conclude that the sometimes permanent visual damage observed in epidemic keratoconjunctivitis might be decreased or eliminated by enhancing the immune response of the infected patient, perhaps during the acute infection.

Summary

Of 120 individuals suffering from follicular conjunctivitis, with or without keratitis, 56 had epidemic keratoconjunctivitis caused by adenovirus type 8. The remaining 64 patients had keratoconjunctivitis produced by several different viruses, including herpes simplex, adenoviruses types 3, 7, 8, 16, 21, and 29, and others. Positive viral cultures were difficult to obtain after the first week of illness in most viral infections. Serologic tests were far more successful in identifying causative agents. Hemagglutination-inhibition tests in adenovirus infections proved to be fast, accurate, and more sensitive than other serologic tests. Among the epidemic and nonepidemic adenovirus groups, the degree of corneal involvement in the infections appeared to be correlated with the level antibody against the infectious agent. Patients with low antibody titers had more severe keratitis than those with high titers. This correlation was true for both the epidemic and nonepidemic patients.

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SECONDARY OCULAR BACTERIAL INFECTION IN HYPOVITAMINOSIS A XEROPHTHALMIA

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Blindness in hypovitaminosis A xerophthalmia is due to the corneal ulceration or perforation that occurs in the advanced stage of keratomalacia. The precise pathophysiology of this condition is still unknown.

Reports on hypovitaminosis A xerophthalmia frequently mention secondary ocular bacterial infection as a contributory factor in the causation of blindness[1-3] but we do not know what these bacterial organisms are or whether they are responsible for producing the corneal changes. We attempted to determine the secondary bacterial infection that occurs during the different stages of xerophthalmia secondary to vitamin A deficiency.

SUBJECTS AND METHODS

During a two-year period from 1972 to 1974, 100 consecutive patients with hypovitaminosis A xerophthalmia were initially seen either at the charity eye clinic or pediatric malnutrition wards and then referred for confirmation and bacteriologic culture of the external eye.

The diagnosis of vitamin A deficiency xerophthalmia was based on the symptom of night blindness and signs of xerosis of the conjunctiva and cornea, Bitot's spots, and keratomalacia. Ocular findings were correlated with physical findings such as malnutrition, gastroenteritis, upper respiratory tract infection, bronchopneumonia, measles, and intestinal parasitism.

Except for infants and uncooperative children, ocular findings were confirmed grossly with a Haag-Streit 900 slit lamp. The severity of the xerophthalmia was graded according to the following criteria: X-0, night blindness; X-1, xerosis of the conjunctiva with or without night blindness and with or without Bitot's spots; X-2, xerosis of the cornea with reversible superficial epithelial changes (Fig. 1); X-3, irreversible corneal changes due to corneal ulceration and keratomalacia (Fig. 2); and

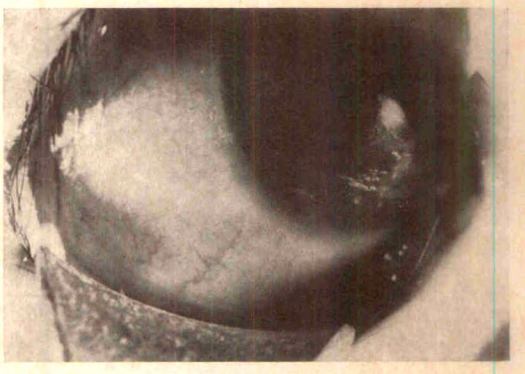


Fig. 1 (Valenton and Tan). Stage 2 xerophthalmia in a 2-year-old child with Bitot's spot and superficial corneal ulceration and xerosis, secondarily infected with *P. aeruginosa.*



Fig. 2 (Valenton and Tan). Stage 3 xerophthalmia in a 2-year-old boy showing conjunctival xerosis, corneal ulceration and infiltration, and hypopyon formation, secondarily infected with *D. pneumoniae.*

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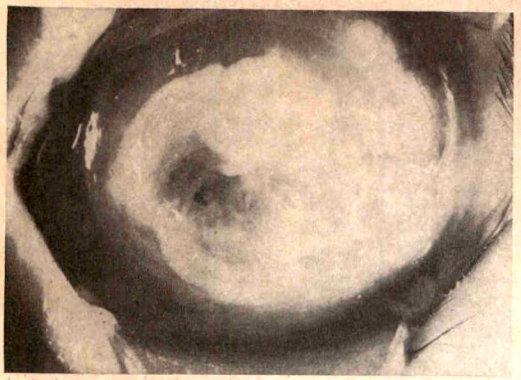


Fig. 3 (Valenton and Tan). Stage 4 xerophthalmia of the fellow eye of the patient in Figure 1, showing corneal perforation secondarily infected with *P. aeruginosa.*

X-4, all previous criteria and corneal perforation (Fig. 3).

We used 10% blood sugar and brain-heart infusion broth as the bacterial culture media. In performing bacterial ocular cultures, one side of a broth-moistened swab was rubbed first over the lower conjunctival cul-de-sac of one eye, and onto one quadrant of a blood agar plate. The same swab was then turned over and rubbed over the lower eyelid margin of the same eye, and onto a second quadrant of the same blood agar plate. We used a second moistened swab to transfer material from the second eye to the plate's third and fourth quadrants. Thus, the four areas of the eyes of one patient were represented on one blood agar plate. The moistened swabs used for each eye were dropped inside two separate tubes containing brain-heart infusion broth. In patients with corneal ulceration or perforation, the cornea was anesthetized with two drops of 0.5% proparacaine hydrochloride ophthalmic solution, rubbed several times with a broth-moistened swab, and placed on one half of another blood agar plate. We dropped the swab into a tube with brain-heart infusion broth. We scraped the ulcer with a Kimura spatula and inoculated the material onto the remaining half of the blood agar plate. The ulcer was again scraped and the material smeared on two glass slides for staining with Gram's and Giemsa stains. The microscopic findings from the scrapings were later correlated with the bacterial culture results.

The plates were then incubated at 37°C for 48 hours and the broth tubes were subcultured after 24 hours in blood agar and Fildes media for *Hemophilus* organisms. The organisms were then identified by colony characteristics and Gram's stain. Biochemical tests were done for the characterization of gram-negative rods.

In this study, normal flora refers to eyelid, conjunctival, and corneal cultures consisting only of *Staphylococcus albus* and diphtheroids. *Hemophilus* species, *Streptococcus viridans, S. aureus,* Mimea-Herellea, *Neisseria* catarrhalis and sicca, Enterobacteriaceae species, and Providence group are all classified as potential pathogens. Usual causes of corneal ulceration such as *Pseudomonas aeruginosa, Diplococcus pneumoniae, Moraxella* species, *St. pyogenes,* and gram-negative rods such as *Klebsiella, Escherichia coli, Alcaligenes faecalis,* and *Proteus* species are classified as pathogens.

The bacterial organism cultured and identified was considered a secondary bacterial infection only when there was semi-confluent to confluent growth of the organism.

Patients who received topically applied antibiotics a week before were all excluded from the series.

Results

There were 57 males and 43 females, ranging from 1½ months to 35 years of age. Eighty-five percent of the patients were younger than 10 years of age. Fifty-eight of the patients were younger than 4 years of age. In the youngest, a 1½-month-old boy, vitamin A deficiency was further confirmed by determination of serum vitamin A level which revealed a value of 8 μg/100 ml of blood (normal, 20 μg). Fifteen patients (15%) were older than 10 years of age, all of whom had ocular findings of nyctalopia and Bitot's spots. In two cases there was an

associated corneal ulceration. Of these 15, three patients older than 20 years of age were lactating mothers. The remaining 12 patients exhibited moderate to severe degrees of malnutrition (Table 1).

We compiled the distribution of patients under the different stages of xerophthalmia (Table 2). There was irreversible corneal involvement in 51 patients (Stages X-3 and X-4). There was corneal ulceration in 29 cases and corneal perforation in 22 cases. Corneal ulceration and perforation were bilateral in 22 cases and five cases, respectively. Most of the 100 patients had one or more of the following systemic conditions: severe malnutrition, 32 cases; acute and chronic gastroenteritis, 59; bronchopneumonia, 21; upper respiratory tract infection, 29; septicemia, two; measles, 12; meningitis, one.

Extraocular bacterial cultures in 100 patients revealed a normal bacterial flora in 14 cases (14%), the presence of potentially pathogenic bacteria in 40 cases (40%), and frankly pathogenic bacteria in 46 cases (46%). Table 3 shows the distribution according to the stage of xerophthalmia and the pathogenicity of the isolated bacteria. With the exception of two patients with corneal ulceration, all patients with either corneal ulceration or perforation harbored potentially pathogenic or pathogenic bacteria. Even in the early stages of xerophthalmia (X-0 to X-2), 75% (37 of 49 cases) already harbored potentially pathogenic or pathogenic organisms.

TABLE 1

AGE GROUPING OF 100 PATIENTS WITH XEROPHTHALMIA

Age Group, yrs	No. of Patients
0– 4	58
5– 9	27
10–19	11
20–35	4

TABLE 2

PATIENTS IN EACH OF THE STAGES OF XEROPHTHALMIA

Stages	No. of Patients
X—0	4
X—1	16
X—2	29
X—3	29
X—4	22

Table 4 shows the type of isolated bacteria, the frequency of isolation, and the number of patients associated with corneal ulceration or perforation. Most patients had mixed flora. The more common bacterial causes of central corneal ulceration or perforation, such as *P. aeruginosa, D. pneumoniae,* and *Moraxella* species, were isolated in 24 cases

TABLE 3

DISTRIBUTION OF 100 PATIENTS ACCORDING TO XEROPHTHALMIA STAGES AND PATHOGENICITY OF ISOLATED BACTERIA

Stage	No. of Patients with Nonpathogens*	No. of Patients with Potential Pathogens†	No. of Patients with Pathogens‡
X—0	0	3	1
X—1	4	9	3
X—2	8	12	9
X—3	2	10	17
X—4	0	6	16
Total	14 (14%)	40 (40%)	46 (46%)

* Nonpathogens are *S. albus* and diphtheroids.

† Potential pathogens are *Hemophilus* species, *St. viridans, S. aureus,* Mimea-Herellea, *Neisseria* catarrhalis and sicca, En. species, and Providence group.

‡ Pathogens are *P. aeruginosa, D. pneumoniae, Moraxella* species, *St. pyogenes, Klebsiella* species, *E. coli, A. faecalis,* and *Proteus* species.

TABLE 4

ISOLATED BACTERIA IN 100 PATIENTS WITH XEROPHTHALMIA ASSOCIATED WITH CORNEAL ULCERATION OR PERFORATION

Microorganisms Isolated	Positive Cases	Patients with Corneal Ulceration	Patients with Corneal Perforation
P. aeruginosa and	9	1	8
E. coli	1	1	0
D. pneumoniae and	7	1	1
Hemophilus species	1	1	0
A. faecalis	1	0	1
E. coli	1	0	1
Moraxella species	4	4	0
A. faecalis and	3	1	0
St. viridans	1	1	0
E. coli and			
S. aureus	2	0	1
St. viridans	1	1	0
Neisseria catarrhalis	1	0	0
Enterobacteriaceae			
species and	1	0	0
St. viridans	2	1	1
S. aureus	1	0	1
Pr. mirabilis	1	0	0
Klebsiella species and			
St. viridans	1	1	0
Providence group and			
St. viridans	1	0	1
Hemophilus			
species and	4	0	1
St. viridans and			
Mimea	1	0	1
St. pyogenes and	2	1	0
Enterobacteriaceae			
species	1	0	0
S. aureus	1	1	0
St. viridans and	11	4	0
Mimea	5	2	1
Neisseria sicca	3	1	1
S. aureus	5	2	1
S. aureus	4	1	2
Neisseria catarrhalis	6	1	0
Mimea-Herellea	4	1	0
S. albus and			
diphtheroids	14	2	0
Total	100	29	22

and were associated with corneal ulceration in eight cases and perforation in 11 cases. *P. aeruginosa* was cultured from 35% of cases with corneal perforation. Less common causes of central corneal ulceration such as *St. pyogenes, Klebsiella* species, *E. coli,* and *A. faecalis* were associated with corneal ulceration in six cases and perforation in one case. Bacterial organisms such as *St. viridans, S. aureus, Neisseria* catarrhalis and Mimea-Herellea, infrequent causes of corneal ulceration or perforation, were associated with corneal ulceration in 13 cases and perforation in eight cases.

DISCUSSION

Acute systemic infection may act as a trigger for the appearance of keratomalacia.[4-6] This raises the question of whether some of the symptoms and tissue changes in man attributed to vitamin A deficiency may actually be caused by bacterial invasion. In this study, eyes were secondarily infected with only 14% of patients harboring a normal flora. One explanation for the many secondary ocular bacterial infections may be that most of these patients had advanced stages of xerophthalmia where host resistance was markedly impaired.

Only two patients with advanced cases of corneal ulceration and perforation had normal flora while the others harbored potentially pathogenic or usually frankly pathogenic bacteria such as *Pseudomonas, Pneumococcus,* and *Moraxella* that cause corneal ulceration and perforation. Most corneal perforations or ulcerations in hypovitaminosis A xerophthalmia may be precipitated by the secondary ocular bacterial infection that follows in its early stages. I do not know how much of the corneal ulceration or perforation is due to hypovitaminosis A xerophthalmia and how much is due to bacterial action. Potential pathogens such as *St. viridans* and *S. aureus* that ordinarily do not invade the cornea may also cause corneal ulceration and perforation due to the lower resistance of the host issue.

SUMMARY

Extraocular bacterial culture was performed in 100 patients with hypovitaminosis A xerophthalmia. There was corneal ulceration in 29 cases and corneal perforation in

22 cases. Eighty-six percent of the patients harbored frankly pathogenic bacteria (46 patients) and potentially pathogenic bacteria (40 patients). All but two patients with either corneal ulceration or perforation harbored potentially pathogenic or frankly pathogenic bacteria. *Pseudomonas aeruginosa, Diplococcus pneumoniae,* and *Moraxella* species were isolated in 37% (19 patients) of cases with corneal ulceration and perforation. I cultured *P. aeruginosa* from 36% (eight patients) of cases with corneal perforation.

The many ocular secondary bacterial infections in the early stages of xerophthalmia seem to suggest that bacterial action plays a major role in causing the corneal ulceration and perforation in hypovitaminosis A xerophthalmia.

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ENDOTHELIAL ALTERATIONS IN CONGENITAL CORNEAL DYSTROPHIES

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Congenital hereditary dystrophies of the corneal endothelium usually manifest pathologic alterations involving the endothelium and Descemet's membrane with secondary stromal and epithelial edema.[1-9] We report the clinical and ultrastructural findings in three different types of congenital endothelial dystrophies: hereditary posterior polymorphous dystrophy (Case 1), congenital hereditary endothelial dystrophy (Case 2), and a nonhereditary congenital endothelial dystrophy (Case 3). Although these three entities are clinically distinct, histologic differentiation is difficult since the response of the corneal endothelium and Descemet's membrane to diverse forms of stimuli is not specific. The patient with posterior polymorphous dystrophy showed an epithelial-like layer of cells on the posterior cornea, an unusual finding that may be specific for this entity and has been documented in only one other published case.[10]

MATERIAL AND METHODS

All corneal buttons were obtained by penetrating keratoplasty. In Cases 1 and 2, the corneas were fixed in 10% formalin, embedded in paraffin, and reprocessed for electron microscopy.[11] In Case 3, one half of the cornea was fixed in 2.5% buffered glutaraldehyde, postfixed in osmium, and embedded in Epon; the other half was fixed in formalin and embedded in paraffin.

Light microscopy—Paraffin sections were stained with hematoxylin-eosin, PAS, toluidine blue, Alcian blue at pH 2.5, colloidal iron, and Masson trichrome stains. Epon-embedded sections, 1 μ thick, were stained with toluidine blue.

Electron microscopy—Ultrathin sections were obtained with an ultramicrotome and were examined with an electron microscope.

CASE REPORTS

Case 1—A 2½-year-old white girl with clouded corneas from birth was first examined here Nov. 24, 1969. The corneas appeared symmetrical. There was a diffuse ground-glass appearance that was equally dense centrally and peripherally (Fig. 1). The corneas showed minimal thickening and mild epithelial edema. The anterior stroma appeared clearer than the posterior, diffusely edematous stroma. Slit-lamp examination of Descemet's membrane showed a distinct band of relucency with numerous irregularities some of which displayed a vesicular appearance. Visual acuity was finger counting at 3 meters in each eye and ocular tension was normal. The clinical diagnosis was posterior polymorphous dystrophy.

A 7.5-mm penetrating corneal transplant was performed in the right eye June 4, 1973. The transplant was clear when the sutures were removed seven weeks after surgery. In October, visual acuity was R.E.: 6/15, and L.E.: counting fingers at 1 meter. On Feb. 23, 1974, a 7.5-mm penetrating corneal transplant was performed in the left eye. At present corrected visual acuity is R.E.: 6/15—2, and L.E.: 6/15+2.

Family history revealed that the child's father had bilateral diffuse corneal opacities in the region of Descemet's membrane and the corneal endothelium (Fig. 2). Some changes were vesicular in appearance, measuring 0.2 to 0.4 mm in diameter. Visual acuity was R.E.: 6/9+3, and L.E.: 6/24—1, and had remained unchanged for the past 35 years. The clinical impression was posterior polymorphous corneal dystrophy. The patient's mother, an 11-year-old sister, and her paternal grandmother had normal corneas.

Light microscopy—RIGHT EYE—The cornea was 0.7 mm thick. The corneal epithelium was irregularly thinned, Bowman's membrane was absent, and the superficial stroma showed irregular alignment of lamellae.

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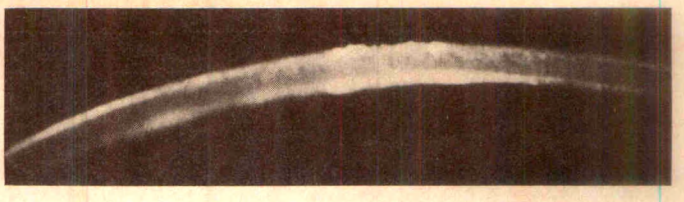


Fig. 1 (Rodrigues and associates). Case 1. Right eye showing full-thickness central stromal changes with opacity of the endothelium and Descemet's membrane.

Descemet's membrane displayed a multilaminar pattern in some areas (Fig. 3, inset) and consisted of an anterior, thin (3 μ), PAS-positive layer that was focally absent in areas, and a posterior, thicker (22 to 30 μ) zone of abnormal collagen. A layer of cells separated Descemet's membrane from the anterior chamber (Fig. 3).

LEFT EYE—The cornea measured 0.5 mm thick. The epithelium showed moderate basal edema. Bowman's membrane was absent. There was superficial stromal fibroblastic proliferation and moderate stromal edema. Descemet's membrane exhibited a multilaminar configuration and was focally absent. It appeared similar to this layer in the right eye and was partially lined posteriorly by a layer of cells. Special stains for acid mucopolysaccharides showed no evidence of abnormal accumulation in both corneas.

Electron microscopy—The findings were similar in both corneal buttons. The corneal epithelium showed minimal basal edema. Bowman's membrane was absent. The collagen fibrils measured 24 to 36 nm in diameter in the midstroma and 40 nm posteriorly with a periodicity of 56 to 60 nm. The spaces between collagen fibers were slightly widened. Descemet's membrane showed an anterior 110- to 120-nm banded portion (Fig. 4). A zone of collagen with scattered areas of 120- to 130-nm banding separated this anterior layer from a posterior thin layer of irregular basement membrane-like material and collagen that displayed long-spacing (110 nm) bundles as well as fusiform sheets of 50- to 56-nm banding (Fig. 4). Paracentrally and peripherally, Descemet's membrane was lined posteriorly by a retrocorneal fibrous membrane and one to two layers of epithelial-like cells (Fig. 3). Myriad microvilli were present on the cell surfaces that faced the anterior chamber (Fig. 3). The lateral cell membranes were connected by numerous desmosomes with prominent tonofilaments (Fig. 3, inset). The cytoplasm showed abundant keratofibrils and few normal cell organelles (mitochondria, Golgi apparatus, and endoplasmic reticulum). There was no evidence of inclusion bodies or of calcification. Centrally, a few endothelial-like cells (Fig. 5) lined an abnormal posterior layer of Descemet's membrane that had a trilaminar pattern (Fig. 5) with an anterior 100- to 110-nm banded area separated by collagen from a posterior layer composed of basement-membrane-like material and fusiform bundles of 55- to 60-nm to 110-nm banded collagen.

Case 2—A 17-year-old white boy had cloudy corneas at birth.[9] Iridencleisis was performed in both eyes at 3 months of age because of presumptive congenital glaucoma based on diffusely clouded corneas at birth. In 1958, visual acuity was R.E.: 6/18, and L.E.: 6/30 and the ocular tension was

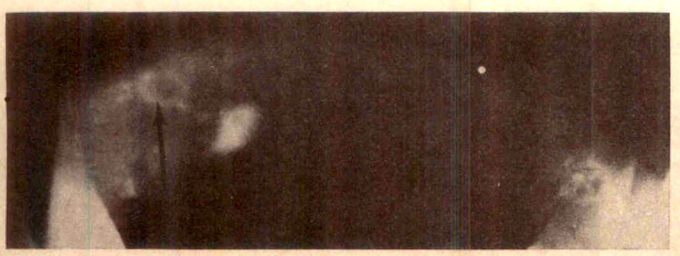


Fig. 2 (Rodrigues and associates). Right eye of the father of Case 1, showing scattered opacities in the cornea, typical of posterior polymorphous dystrophy. Vesicular lesions were seen on slit-lamp examination (arrow).

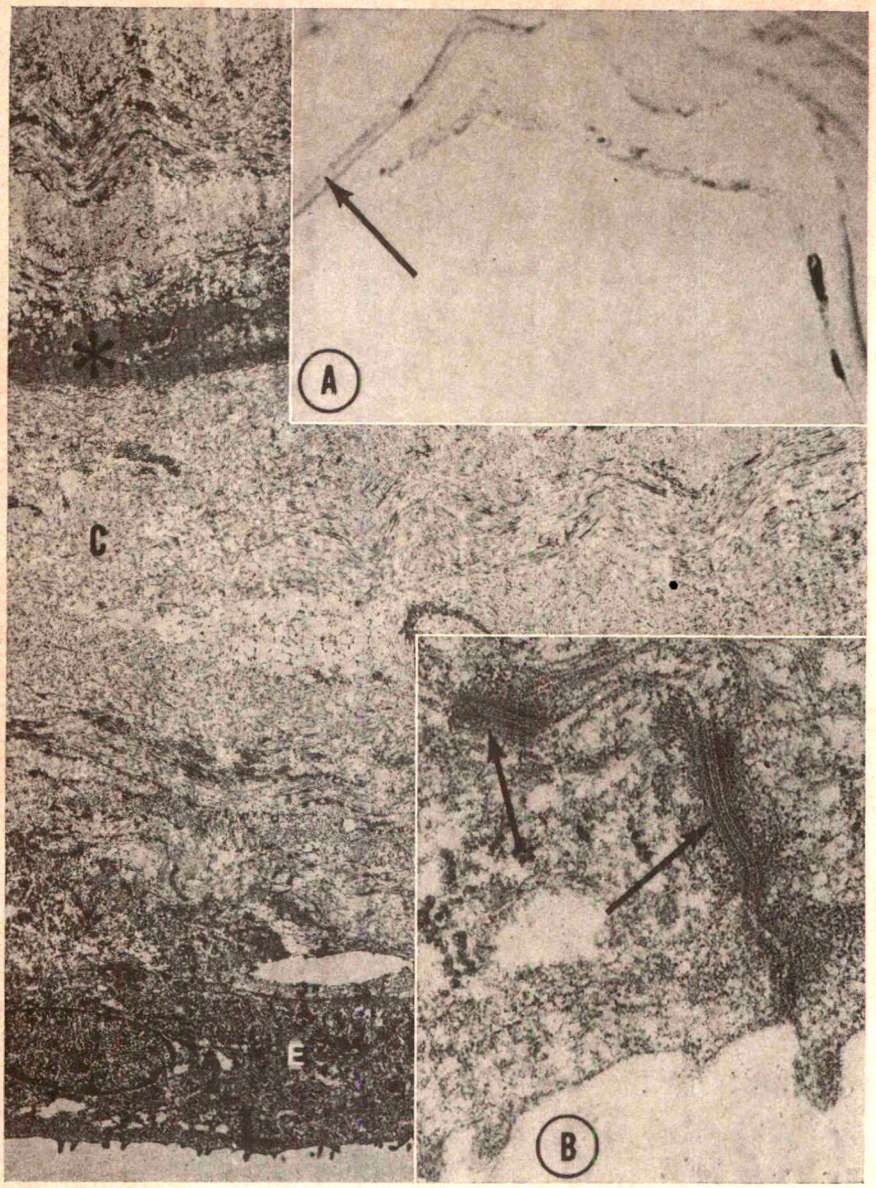


Fig. 3 (Rodrigues and associates). Fragments of basement membrane-like material (asterisk) seen in a collagen matrix (C). A layer of epithelial-like cells (E) with microvilli faces the anterior chamber (×5,240). Inset A, Multilaminar Descemet's membrane with a thin dense anterior layer (arrow), adjacent collagen, and a few cells (×64). Inset B, Desmosomes (arrows) connecting lateral cell membranes in the posterior epithelial-like cell layer (×53,000).

normal. The corneas were hazy (Fig. 6) and thickened, and diffuse epithelial and stromal edema obscured visualization of the posterior cornea. In 1962, the corneal haziness had increased and visual acuity was R.E.: 2/60, and L.E.: 3/60. A 7.5-mm penetrating keratoplasty was performed in the left eye. Two years later, visual acuity was R.E.: finger counting, and a 7-mm penetrating keratoplasty was performed in that eye. In 1973, he had a clouded graft in his right eye and a partially clouded graft in the left eye.

Urinalysis showed no abnormal increase in mucopolysaccharides. There was no history of systemic disease. Two brothers had similar con-

genital corneal edema, erroneously diagnosed as congenital glaucoma. The parents, grandparents, and three sisters were not affected.

Light microscopy—The cornea of the right eye was 1 mm thick. The epithelium was thinned with edema of the basal layer. Bowman's membrane was absent and marked stromal edema was observed. Descemet's membrane was thickened (Fig. 7, inset) and was 23 μ wide. There were a few flattened endothelial cells containing pigment granules. Special stains for mucopolysaccharides showed no evidence of abnormally increased accumulation.

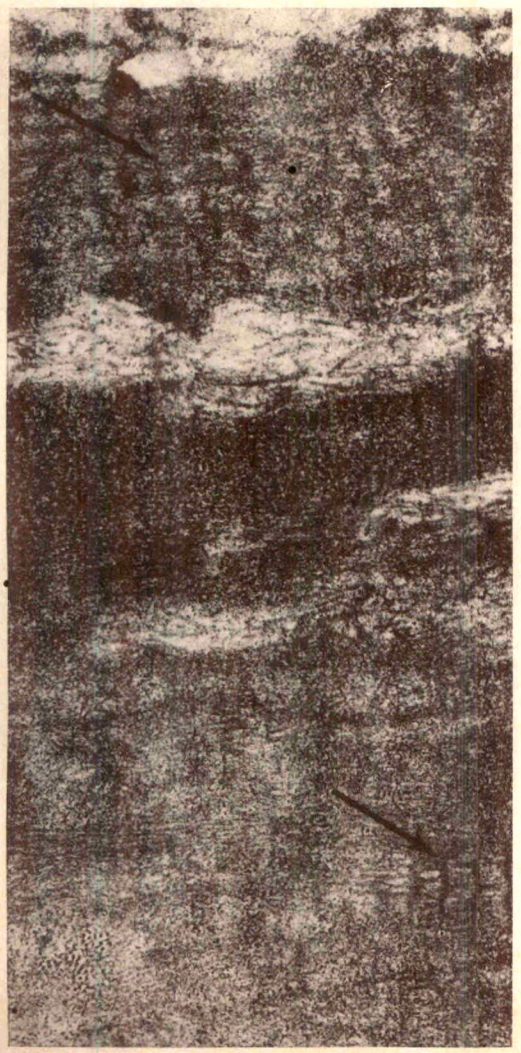


Fig. 4 (Rodrigues and associates). Descemet's membrane displays normal anterior and abnormal posterior banded areas (arrows) separated by collagen (×12,600).

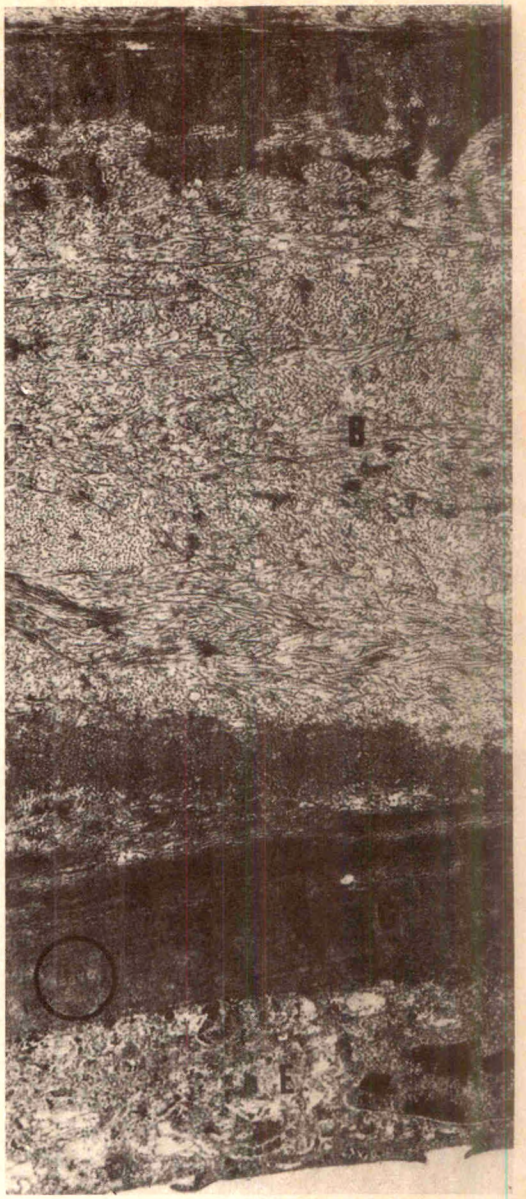


Fig. 5 (Rodrigues and associates). A layer of endothelial-like cells (E) lines the posterior corneal surface. Descemet's membrane shows an anterior banded zone (A), intermediate collagen (B), and a posterior layer (C) of basement membrane-like material and collagen, including 110-nm banded areas (circle) (×11,000).

Electron microscopy—The epithelial basement membrane and Bowman's membrane were absent in the corneal button of the

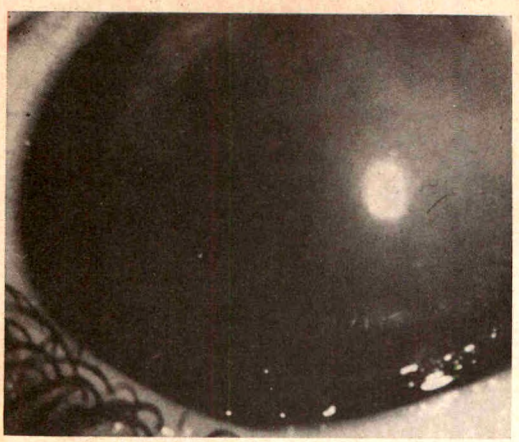


Fig. 6 (Rodrigues and associates). Case 2. Left eye showing ground-glass corneal opacification.

right eye. The collagen fibrils were 30 to 26 nm in diameter in the midstroma, 40 to 50 nm anterior to Descemet's membrane, and showed a periodicity of 58 to 60 nm. The stromal keratocytes had distended rough endoplasmic reticulum and swollen mitochondria. The interfibrillar spaces were widened. Descemet's membrane was 23 μ thick. The anterior portion was 3 μ wide and displayed 100- to 110-nm banding (Fig. 7). The abnormal posterior layer was 20 μ thick. In the midportion and posterior part of Descemet's membrane, there were fusiform bundles of collagen with 50- to 60-nm banding and collagen fibrils with a diameter of 35 to 40 nm (Figs. 8 and 9) with interspersed basement membrane-like material. A few areas of 100- to 110-nm banding were noted in the posterior portion of Descemet's membrane. The endothelial cells were scant, attenuated, and contained melanin pigment granules.

Case 3—A 5-year-old white girl was born on June 4, 1967, seven weeks before term due to premature separation of the placenta. The delivery was normal and the child weighed 1,792 g (4 lbs) at birth. When she failed to walk at 2 years, a neurologic examination revealed only abnormal station and gait. She had decreased muscle mass of the arms and legs and contractures of the knees. Roentgenograms at that time showed no abnormality of the joints, lower spine, or other bony changes. A tentative diagnosis of juvenile rheumatoid arthritis was made. On March 2, 1973, we noted bilateral hazy corneas (Fig. 10) and increased pressure in the left eye and normal pressure in the right eye. There was epithelial and stromal edema of the inferior two thirds of the right cornea and diffuse edema of the entire left cornea. The anterior chamber could not be clearly seen. A goniopuncture was performed April 6 in the left eye.

On June 8, ocular examination revealed normal ocular tensions in each eye. The lower two thirds of the right cornea showed microcystic epithelial edema with moderate stromal edema. The deep stroma at the level of Descemet's membrane was diffusely gray and the endothelium could not be seen clearly. Visual acuity was R.E.: 6/30, and L.E.: finger counting. On Nov. 5, systemic examination elsewhere revealed signs and symptoms compatible with inactive dermatomyositis. Visual acuity was R.E.: 6/120, and L.E.: counting fingers because of marked corneal edema. A 7.5-mm penetrating corneal transplant was performed in the left eye in March 1974. Slit-lamp examination of her parents and two siblings showed normal results.

Light microscopy—The cornea was 1 mm

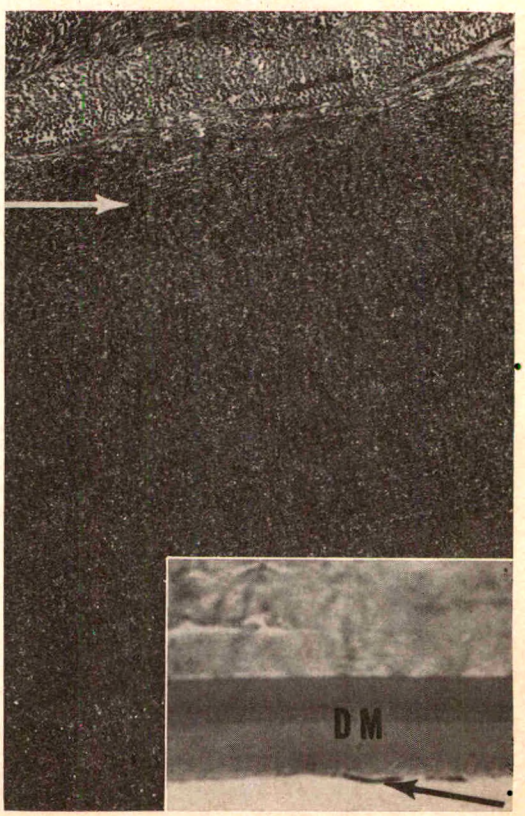


Fig. 7 (Rodrigues and associates). Case 2. Right eye showing normal anterior banding of Descemet's membrane (arrow) (×14,600). Inset, Multilaminar thickening of Descemet's membrane (DM) and sparse atrophic endothelial cells (arrow) (×640).



Fig. 8 (Rodrigues and associates). The mid-portion of Descemet's membrane shows fusiform bundles of banded collagen (arrow) (×45,000).

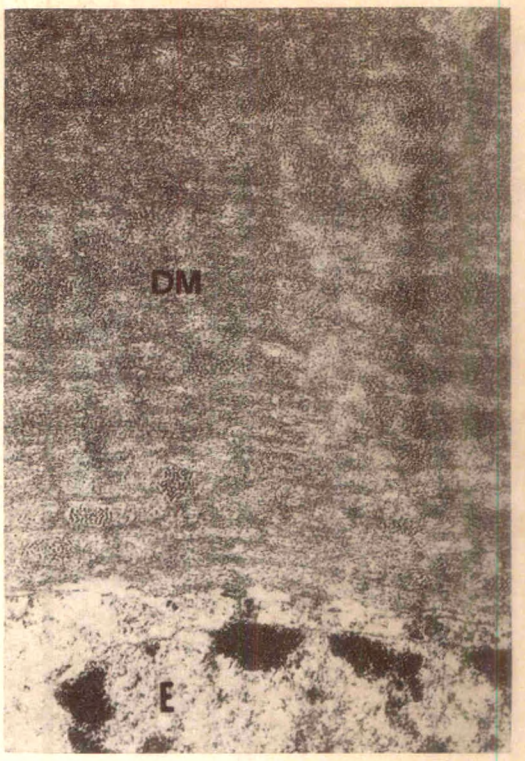


Fig. 9 (Rodrigues and associates). Posterior portion of Descemet's membrane (DM) with collagen fibrils and basement membrane-like material. An endothelial cell (E) is adjacent to Descemet's membrane (×18,000).

thick. Minimal epithelial edema was present. Bowman's membrane was focally absent and areas of superficial stromal fibrosis and marked stromal edema were observed. Descemet's membrane was 20 μ thick. An irregular retrocorneal fibrous membrane was present (Fig. 11, inset). Stains for mucopolysaccharides showed no increased accumulation.

Electron microscopy—The corneal epithelium showed minimal basal intracellular edema. Bowman's membrane displayed the usual random orientation of collagen fibrils and was absent in some areas. The diameter of the collagen fibrils was 15 to 25 nm in the midstroma and 35 to 40 nm in the posterior stroma. Descemet's membrane consisted of an anterior 100- to 110-nm banded portion measuring 2.5 μ thick (Fig. 12) and a posterior nonbanded zone measuring 17.5 μ. The latter had fusiform bundles of 50- to 55-nm banded collagen with interspersed basement membrane-like material and focal areas of 100- to 110-nm banded collagen (Fig. 13, inset). Although the endothelium

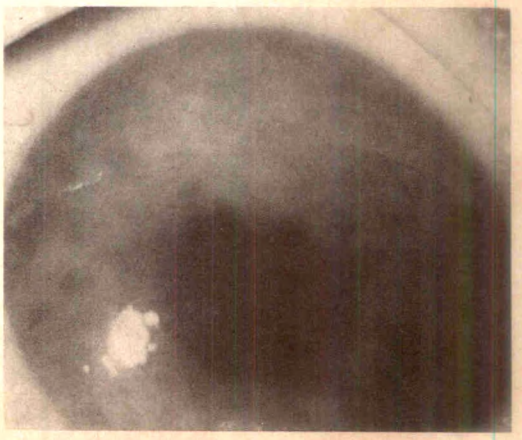


Fig. 10 (Rodrigues and associates). Case 3. Left eye showing diffusely hazy cornea with epithelial and stromal edema.

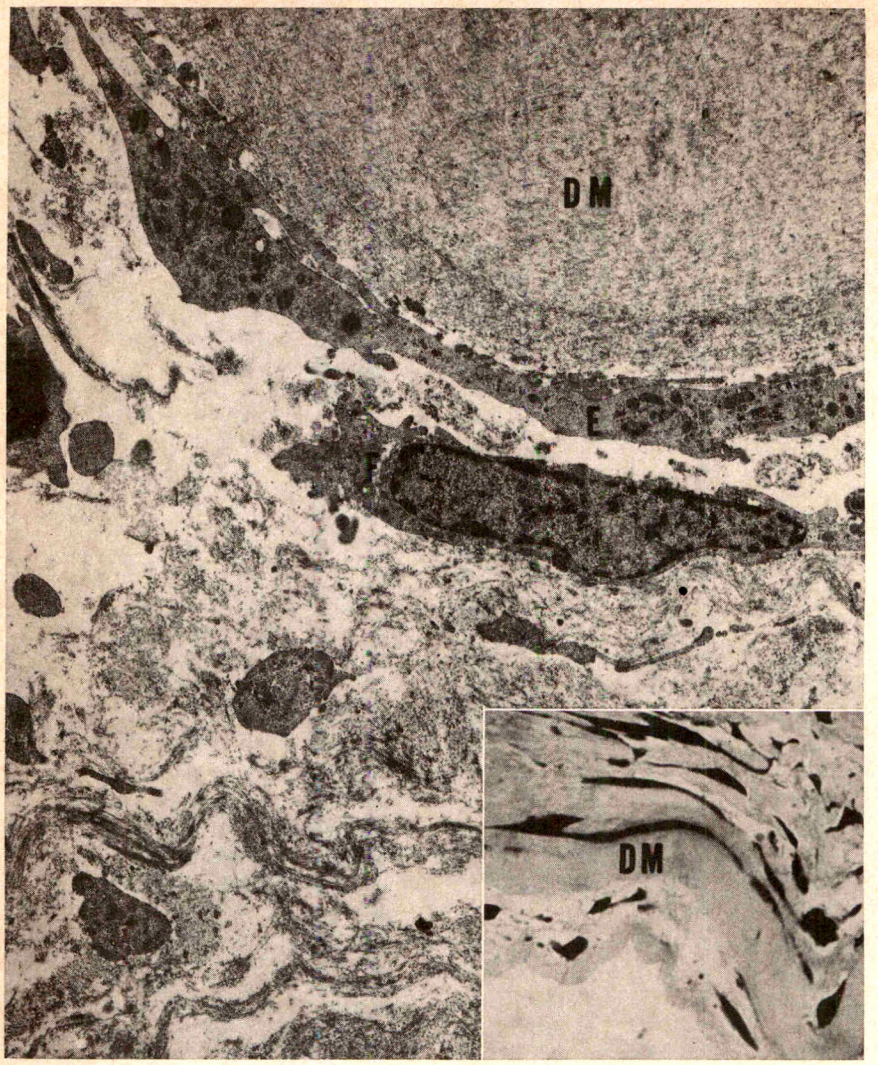


Fig. 11 (Rodrigues and associates). The posterior portion of the original Descemet's membrane (DM) is lined posteriorly by collagen, abnormal endothelium (E), and fibroblast-like cells (F) (×6,600). Inset, Original Descemet's membrane (DM) and a retrocorneal fibrous membrane are seen (×640).

was partially replaced by a retrocorneal fibrous membrane, scattered attenuated endothelial cells with lateral junctions were seen (Fig. 13).

Discussion

Posterior polymorphous dystrophy is an unusual bilateral hereditary condition characterized clinically by opacities localized to Descemet's membrane and endothelium.[12] Four histopathologic studies of this entity have been reported.[10,13–15] Morgan and Patterson[13] described PAS-positive excrescences of Descemet's membrane lined by a thin layer of endothelium. In Hanselmayer's patient,[15,16] Descemet's membrane was multilaminar with interspersed collagen and displayed excrescences. The endothelium was mostly absent and the few remaining cells showed degenerative changes. Hogan and Bietti[14] reported a case of presumably the same condition in a 47-year-old man. Descemet's membrane exhibited guttate excrescences and there were calcium deposits in



Fig. 12 (Rodrigues and associates). Descemet's membrane exhibits a normal anterior banded zone with long-spacing 110-nm collagen (top arrow) and adjacent fusiform bundles of 50- to 55-nm banded collagen (bottom arrow) (×22,000).

the deep corneal stroma. These findings suggest an endothelial dystrophy rather than the hereditary posterior polymorphous type.

In our first patient (Case 1), Descemet's membrane was thickened and multilaminar and composed of two thin layers of basement-membrane-like material separated by collagen that also formed a retrocorneal membrane. Excrescences were not observed in serial sections and in some areas Descemet's membrane was lacking. Electron microscopy revealed a normal anterior portion with 100- to 110-nm banding, posterior collagen fibrils, and basement-membrane-like material. The abnormal posterior layer of Descemet's membrane showed fusiform bundles with a less well-defined 50- to 100-nm banding. Abnormal 100- to 110-nm banding of the posterior portion of Descemet's membrane was also seen in Cases 2 and 3, and has been observed in congenital corneal endothelial dystrophy,[7] hereditary corneal edema,[17] Fuchs' dystrophy,[18] and in other corneal diseases.[12] Centrally, Descemet's membrane was lined by a few degenerated endothelial cells. Paracentrally and peripherally the posterior layer was

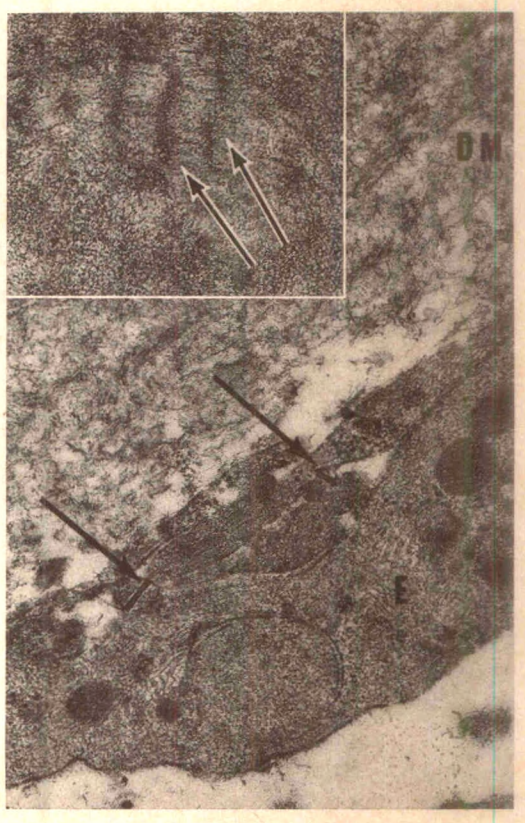


Fig. 13 (Rodrigues and associates). An abnormal endothelial cell (E) lining the posterior portion of Descemet's membrane (DM) shows lateral junctions (arrows) and intracytoplasmic filaments. Inset, Abnormal 100-nm banding (arrows) in the posterior portion of the original Descemet's membrane (×30,250).

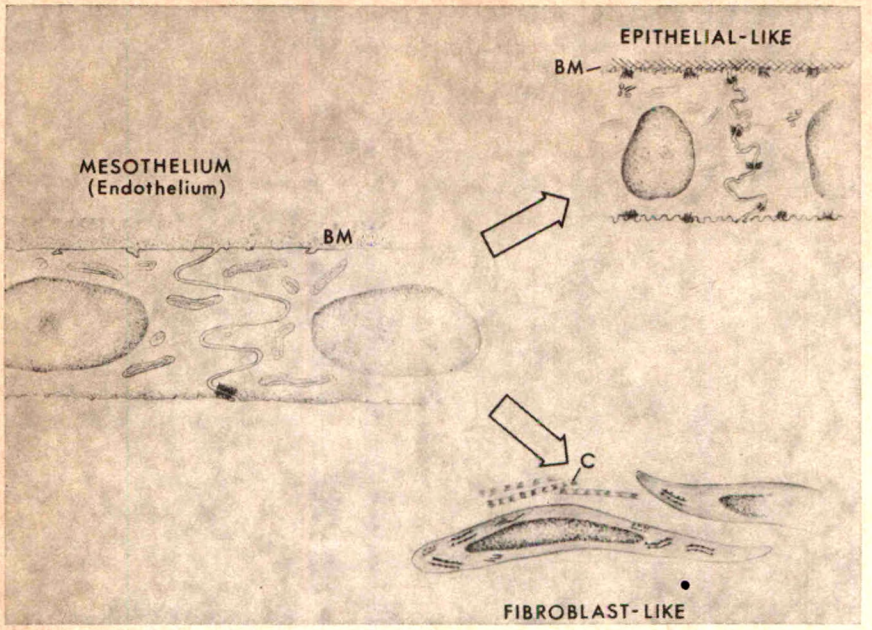


Fig. 14 (Rodrigues and associates). The endothelial (mesothelial) cell is characterized by a junctional complex, a thick basement membrane (BM), pinocytotic vesicles, prominent mitochondria and decreased Golgi, and rough endoplasmic reticulum. It may occasionally undergo transformation to fibroblast-like cells with collagen (C), filaments, subcortical densities, increased rough endoplamic reticulum and Golgi, and decreased mitochondria, or to epithelial-like cells with desmosomes, surface microvilli, keratofibrils, and basement membrane.

formed by epithelial-like cells with desmosomal lateral junctions, tonofibrils, and prominent cytoplasmic filaments. Microvilli faced the anterior chamber. Boruchoff and Kuwabara[10] reported one case with similar findings. They postulated that the origin of the epithelium on the posterior corneal surface could have been an embryonal displacement of the epithelial cells into the anterior chamber, or the result of an unspecified developmental disorder.

We believe that another explanation is more likely. Since the endothelium is actually a mesothelial layer,[19] it is capable of conversion to cells with epithelial characteristics (Fig. 14). This has been documented in tissue culture studies of endothelial cells of the cornea,[20] as well as in Fuchs' dystrophy[18,21] and hereditary corneal edema.[22]

Ultrastructural studies of normal mesothelium of mice and rats[23,24] have shown that mesothelial cells have features more characteristic of epithelial cells than of fibroblasts. They appear flattened, rest on a continuous basement membrane, and display complex intercellular attachment and microvilli. Benign[24] and malignant[25,26] mesotheliomas of the pleura may have characteristics of epithelial cells as well as of fibroblasts. Desmosomes have been observed in mesothelial cells (meningothelial) of the arachnoid.[27]

Occasional poorly developed desmosomes have been described in normal human corneal endothelium.[28] Thus, the endothelium is truly a pluripotential mesothelium capable of transformation into cells with fibroblast-like, as well as epithelial-like, characteristics (Fig. 14). The layers of collagen may represent embryonic markers, thus accounting for the trilaminar appearance of Descemet's membrane. Presumable endothelial-like cells form fetal Descemet's membrane composed of the normal 100- to 110-nm

banded zone. These may have converted to fibroblast-like cells forming the central collagenous area. Subsequently, transformation to epithelial-like cells could have resulted in the more typical posterior layer of basement membrane-like material. These ultrastructural findings may be specific for hereditary posterior polymorphous dystrophy.

In Case 1, there was no history of prior trauma or surgery that could account for the abnormally located epithelial-like cells on the posterior corneal surface. Similar observations in two cases of hereditary posterior polymorphous dystrophy have been documented by transmission and scanning electron microscopy by Grayson,[29] who described associated mesodermal dysgenesis (posterior keratoconus, sclerocornea, Axenfeld's anomaly, and Rieger's anomaly). We did not see such defects in our patient. In Case 2, there is clinical and histologic evidence of congenital hereditary endothelial dystrophy. The thickened multilaminar Descemet's membrane was the result of an abnormal posterior layer of collagen. There was marked stromal edema and less epithelial edema. Similar observations have been reported in previous studies of this entity.[5,7]

The findings in Case 3 did not conform to any previously described specific clinical entity, and the histologic examination did not further elucidate the nature of the disorder. These findings have also been noted in postinflammatory conditions, particularly in interstitial keratitis[30] and following trauma,[31] and are indicative of the nonspecific response of the endothelium to many corneal diseases.

Although our cases are examples of separate corneal conditions that are recognized clinically, histologic differentiation was not difficult in the case of hereditary posterior polymorphous dystrophy that probably represents a specific entity. An excessive amount of Descemet's membrane is produced by regenerating endothelium, following diverse stimuli such as trauma, inflammation, infection, degeneration, or toxins. The thickened multilaminar membrane results from production of new Descemet's membrane that contains small and large collagen fibrils, 50- to 100-nm banded fibrillar material, and amorphous basement-membrane-like material. This is located posterior to the original Descemet's membrane and fibroblast-like cells may line its posterior surface.[32] Fibroblastic metaplasia has also been observed in tissue cultures of embryonic chick endo-

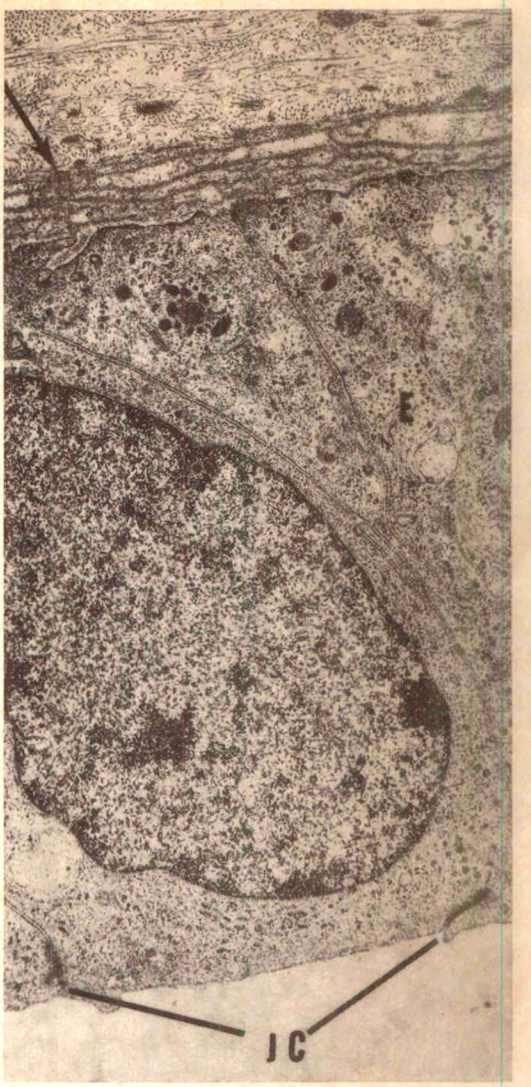


Fig. 15 (Rodrigues and associates). Human fetal cornea at 24 weeks' gestation. Focal banding (arrow) is demonstrated in the anterior portion of Descemet's membrane. The endothelial cells (E) are connected by junctional complexes (JC) (×11,000).

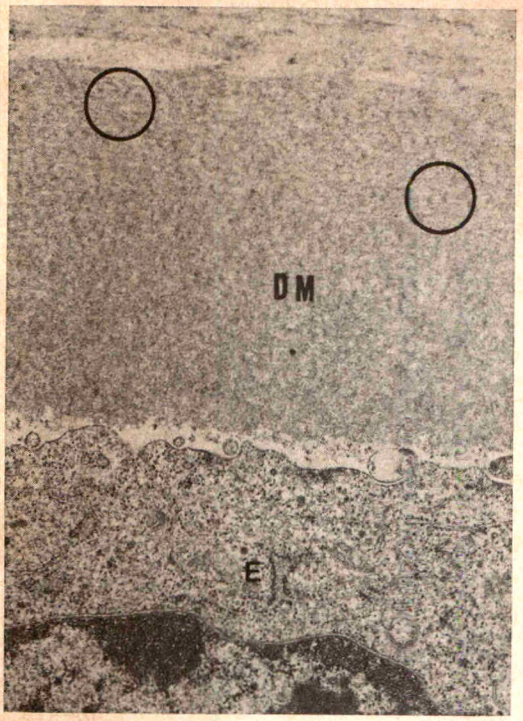


Fig. 16 (Rodrigues and associates). Human fetal cornea at 40 weeks' gestation. Descemet's membrane (DM) displays the typical banded pattern (circles) overlying the normal endothelium (E) (×15,880).

thelial cells.[33] Occasionally, the endothelial cells may respond to certain insults with the characteristics of mesothelial cells, as demonstrated in Case 1.

The endothelial transformation (metaplasia) in our patients probably occurred after 20 weeks' gestation since the anterior banded portion of Descemet's membrane was observed in all three cases. In a normal human fetal cornea that was studied at 24 weeks' gestation, focal anterior banding was evident in Descemet's membrane, but the membrane showed many segments of nonbanded basement-membrane-like material (Fig. 15). In a fetal cornea at 40 weeks' gestation, an anterior banded pattern and a posterior nonbanded zone were observed (Fig. 16). A fetal cornea at 12 weeks' gestation showed no evidence of banding. Wulle[34] made similar observations.

Summary

We studied the clinical and ultrastructural findings in three different types of congenital endothelial dystrophies: hereditary posterior polymorphous dystrophy, congenital hereditary corneal dystrophy, and a nonhereditary congenital endothelial dystrophy.

In the first patient, with hereditary posterior polymorphous dystrophy, a layer of epithelial-like cells was observed adjacent to endothelial cells on the posterior corneal surface. Descemet's membrane displayed a multilaminar pattern and consisted of an anterior, thin (3 μ), PAS-positive layer and a posterior, thicker (25 to 30 μ) zone of abnormal collagen. The second patient, with congenital hereditary endothelial dystrophy, showed a thickened multilaminar Descemet's membrane and scant endothelial cells. In the third patient with nonhereditary congenital endothelial dystrophy, the thickened Descemet's membrane was lined posteriorly by a retrocorneal fibrous membrane. A few degenerated endothelial cells were present. All three cases showed 100- to 110-nm banding posteriorly.

In these three clinically distinct entities, electron microscopy was useful in demonstrating the unusual form of endothelial transformation to epithelial-like cells in one patient, in contrast to the more common fibroblast-like metaplasia of endothelial cells seen in the other two patients.

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HEMOLYTIC GLAUCOMA

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Hemolytic glaucoma, an uncommon variety of secondary open-angle glaucoma occurring in eyes recently afflicted by intraocular hemorrhage, was first described by Fenton and Zimmerman[1] in 1963. Their report concerned an eye which had developed acute intractable glaucoma three weeks after a large vitreous hemorrhage. When they examined the eye histopathologically, they found many large macrophages stuffed with pigment filling its anterior chamber and infiltrating its trabecular meshwork. These large cells, together with extracellular debris (pigment and fragments of hemolyzed red cells), appeared to have blocked the trabecular pathways for outflow of aqueous humor. Similar macrophages, pigment, and disintegrating red blood cells filled the vitreous cavity.

Using special staining techniques, including the Prussian blue reaction before and after microincineration, the authors identified the pigment in the debris and in the macrophages to be hemoglobin. The authors suggested that hemoglobin-filled macrophages, free hemoglobin, and remnants of lysed red blood cells had been carried from the vitreous cavity to the chamber angle by the aqueous circulation. In the trabecular meshwork, the large cells had become entrapped, blocking aqueous outflow, and causing the intraocular pressure to rise. The similarity of this condition to phacolytic glaucoma, in which the trabecular meshwork is blocked by macrophages filled with lens protein, caused Fenton and Zimmerman to propose the analogous name of hemolytic glaucoma.

Two additional cases of hemolytic glaucoma have since been reported[2,3]; in each the clinical presentation and histologic features were identical to the first case. Furthermore, a hemolytic mechanism was probably responsible for the glaucoma in one of a group of patients described in 1960 by Vannas.[4] Her patient had developed acute glaucoma three weeks after a large vitreous hemorrhage and small hyphema; histopathologic examination revealed the trabecular meshwork to be infiltrated by macrophages filled with iron pigment.

Because of its infrequent occurrence and the scarcity of published case reports, hemolytic glaucoma remains a condition with which many ophthalmologists are unfamiliar. In this paper we describe the clinical features of five patients with presumed hemolytic glaucoma, suggest criteria for its diagnosis, and propose a plan for its treatment.

CASE REPORTS

Case 1—This 60-year-old man was blind in his right eye from an old retinal detachment. His left eye was examined yearly for 15 years because of a gradually worsening cataract and minimally elevated intraocular pressures (20 to 22 mm Hg).

On Dec. 6, 1973, the cataract was extracted and a sector iridectomy was made. The operation and immediate postoperative course were uneventful. Twelve days after his operation, he rubbed his left eye and suddenly lost vision. When examined two days later, he had a small hyphema, a large vitreous hemorrhage, and intraocular pressure of 6 mm Hg. The hyphema soon absorbed, but the vitreous hemorrhage persisted, obscuring his vision and our view of his retina.

On Jan. 4, 1974, 17 days after the hemorrhage, the intraocular pressure suddenly increased to 32 mm Hg. His chamber angle was wide open, the inferior trabecular meshwork appeared bright red, and the remaining meshwork was reddish-brown. Treatment with acetazolamide and mannitol was ineffective in decreasing the pressure; it continued to increase, reaching 54 mm Hg. A diagnosis of hemolytic glaucoma was made, and on Jan. 11, the anterior chamber was evacuated and irrigated through a corneal paracentesis incision.

The anterior chamber washout lowered the intraocular pressure for three days; on the fourth day it again increased to 40 mm Hg. On Jan. 16, the anterior chamber was again irrigated. Cytologic examination of an aliquot of aqueous humor revealed macrophages stuffed with granules of golden brown pigment (Fig. 1) and others containing larger

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globules, perhaps hemoglobin or intact red blood cells (Fig. 2).

The patient has slowly improved. Intraocular pressure has remained under 30 mm Hg, and the vitreous hemorrhage has gradually resorbed. Visual acuity has improved to 20/30.

Case 2—This 76-year-old woman first attended our clinic on April 6, 1972, complaining of pain in her right eye. She had a history of cataracts, worse in her right eye, and five months previously had been briefly treated with eyedrops for elevated pressure and inflammation in her right eye.

Visual acuity was R.E.: light perception, and L.E.: 20/50. Intraocular pressure was R.E.: 69 mm Hg, and L.E.: 19 mm Hg. In the right eye the cornea was edematous, the aqueous humor contained many red blood cells, the lens had a dense brunescent nuclear cataract, and the chamber angle was open. The left eye had an early cataract. Ultrasound examination of the right eye revealed a dense vitreous hemorrhage but no retinal detachment.

Treatment with acetazolamide, topically applied epinephrine, and miotics rapidly decreased the pressure to a normal level. A year later, after an attempt to stop treatment with acetazolamide, intraocular pressure in her right eye was 50 mm Hg, quickly decreasing again with reinstitution of acetazolamide treatment. However, several months later she returned with an intraocular pressure of 54 mm Hg despite maximum medical treatment. Red blood cells were still floating in her aqueous humor, and reddish-brown pigment was visible in the trabecular meshwork. The vitreous hemorrhage persisted. Blood tests for diabetes and bleeding disorders were negative.

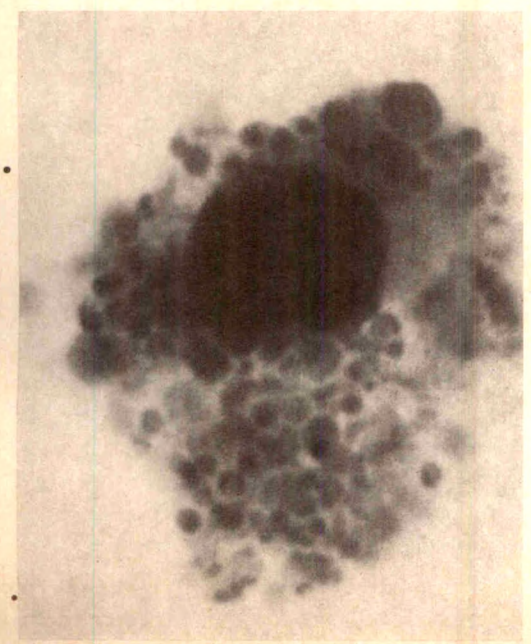


Fig. 1 (Phelps and Watzke). Case 1. Macrophage from aqueous humor filled with small golden granules, probably hemosiderin (Papanicolaou's stain, ×2,500).

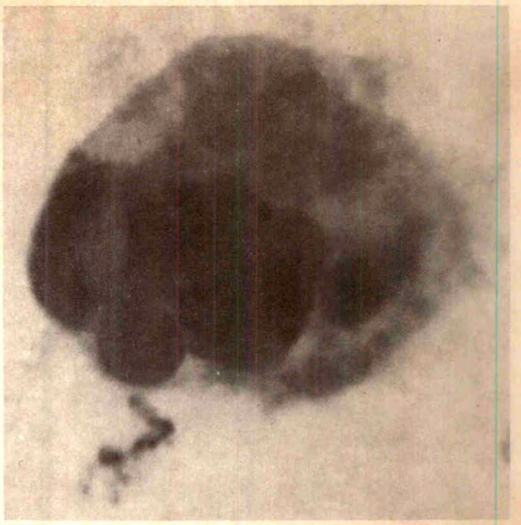


Fig. 2 (Phelps and Watzke). Case 1. Macrophage from aqueous humor containing reddish-brown globules that may be hemoglobin or whole red blood cells (Papanicolaou's stain, ×2,500).

On Feb. 15, 1974, in preparation for a vitrectomy, the right cataract was extracted. Postoperatively the intraocular pressure was elevated but decreased to 9 mm Hg within two weeks. During this time the aqueous humor became clear of red blood cells for the first time. Ophthalmoscopic examination now revealed many vitreous membranes, but through them the optic disk was pale and totally cupped. Her visual field was restricted to a small temporal island. No source for the vitreous hemorrhages could be seen.

Six months later, after recurrence of the vitreous hemorrhage, intraocular pressure was elevated, and again responded to medical treatment.

Case 3—This 64-year-old man awoke from a nap on Aug. 13, 1970, with no vision in his right eye. Five days later, we found a clear anterior chamber, intraocular pressures of 13 mm Hg in both eyes, and a dense vitreous hemorrhage in the right eye. After three days of bedrest, the retina could be seen only in the superior periphery.

He returned 15 days later. Although he had no pain, intraocular pressure in his right eye had increased to 43 mm Hg. The right anterior chamber contained some freely moving red blood cells, the chamber angle was open, no rubeosis was visible, and reddish pigment was deposited on the trabecular meshwork. The fundus was still not visible because of vitreous blood.

Treatment with acetazolamide was begun. Two weeks later, intraocular pressure was 13 mm Hg, and the anterior chamber contained no cells. One month later, after a week of no treatment, intraocular pressures were R.E.: 18 mm Hg, and L.E.:

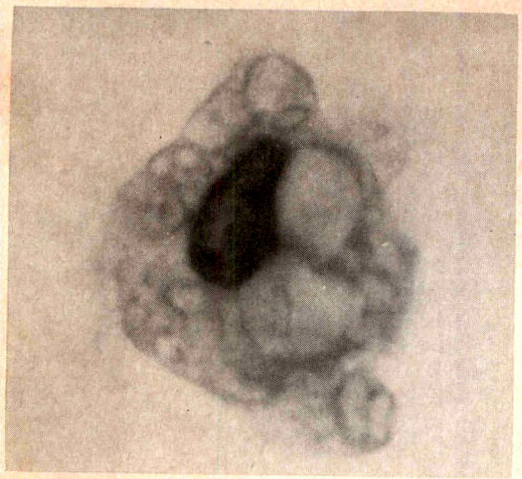


Fig. 3 (Phelps and Watzke). Case 5. Macrophage from aqueous humor filled with golden-brown granules and a few larger inclusions (Papanicolaou's stain, ×2,500).

11 mm Hg. The anterior chamber again contained some small reddish blood cells. Ultrasound now revealed a total retinal detachment, not present on earlier examinations. Because the retina could not be seen, we did not attempt surgical repair of the detachment.

We observed the patient for six more months. His intraocular pressure remained normal, and the vitreous hemorrhage did not clear.

Case 4—This 43-year-old woman suddenly lost vision in her right eye Feb. 1, 1967. Six years previously she had had extensive surgery and irradiation for a carcinoma of her right ethmoid sinus. The tumor had not recurred, her eye had been uninvolved, and she had been examined by us in 1962 with no retinal abnormalities noted.

She had a dense vitreous hemorrhage in the right eye. Intraocular pressure was R.E.: 9 mm Hg, and L.E.: 13 mm Hg. One week later, intraocular pressure was R.E.: 8 mm Hg, and L.E.: 12 mm Hg.

On Feb. 17, she awoke with severe pain in her right eye. Intraocular pressure was 30 mm Hg, the chamber angle was open, and we saw no rubeosis.

Treatment was begun with acetazolamide. One week later, intraocular pressure was 42 mm Hg; however, within a month it had decreased to 8 mm Hg. It remained low, even without treatment. Ten months later the vitreous hemorrhage had not cleared, and the eye was becoming phthisical.

Case 5—This 48-year-old man was chopping wood when a small branch struck his right eye, causing him to lose vision. Examination revealed a 6-mm clot extending upward from the inferior angle and a 3-mm hyphema. Two days later the hyphema was smaller; however, intraocular pressure was in the range of 40 and 50 mm Hg where it remained, despite treatment with corticosteroids, epinephrine, miotics, acetazolamide, glycerol, and mannitol.

We saw the patient in consultation nine days after his injury. The hyphema was less than 1 mm. The central clot persisted, but most of the anterior chamber contained aqueous humor. The intraocular pressure was 43 mm Hg, and the cornea was edematous. After topical application of glycerin, his cornea was clear and by gonioscopy, the chamber angle was open and mostly free of blood or clot. The trabecular meshwork was reddish-brown. The hyphema and part of the blood clot were washed out of the anterior chamber. An aliquot of aqueous humor was centrifuged, and the sediment was embedded and sectioned; pigment-containing macrophages were found. His intraocular pressure was decreased for two days and then increased to 41 mm Hg. The anterior chamber was again irrigated. The whole clot broke up, and the chamber became completely clear. A sample of aqueous humor, passed through a Millipore filter, contained red blood cells, a few lymphocytes, and some large cells filled with golden pigment granules (Fig. 3). Intraocular pressure remained under 20 mm Hg since the second irrigation. Thus, a hemolytic mechanism may have been partially responsible for the glaucoma.

Discussion

Hemolytic glaucoma is a rare form of open-angle glaucoma that typically begins several days to weeks after a large intraocular hemorrhage. The onset of the glaucoma depends on when hemolysis begins in the hemorrhage. In experimental vitreous hemorrhages, hemolysis starts by the fifth day and continues for ten to 12 more days.[5–7] In pathologic hemorrhages, recurrent bleeding may permit the hemolytic process to continue indefinitely.

Hemoglobin, released from hemolyzed red blood cells, can be eliminated from the eye by at least three mechanisms. It may be carried as free hemoglobin by the aqueous humor through the trabecular meshwork and into the systemic circulation.[8] It may be phagocytized by macrophages that also are carried out of the eye by the circulation of the aqueous humor. It may be degraded into globin, bilirubin, and iron while still in the vitreous cavity.[9]

Hemolytic glaucoma occurs if the trabecular passages for aqueous outflow become clogged by hemolytic debris (fragments of lysed red blood cells, hemoglobin, and hemoglobin-filled macrophages). The volume of hemolytic debris presenting to the meshwork is probably a critical factor in determining

whether or not glaucoma will develop. In all published cases of hemolytic glaucoma and in four of our patients (Cases 1-4), the antecedent vitreous hemorrhage was large.

In the differential diagnosis, hemolytic glaucoma must be clearly distinguished from two other varities of secondary glaucoma: hemosiderotic glaucoma and neovascular (hemorrhagic) glaucoma.

Hemosiderotic glaucoma is a secondary open-angle glaucoma that develops slowly and insidiously in an eye with a long history of recurrent intraocular hemorrhages. Like hemolytic glaucoma, it is a consequence of hemolysis, but its pathogenesis is different. As noted previously, some of the hemoglobin released into the eye during hemolysis is degraded into globin, bilirubin, and iron. Various tissues of the eye, including the trabecular endothelium, receive the iron. If the normal apoferritin-ferritin system for intracellular storage of iron becomes saturated, toxic granules of inorganic iron known as hemosiderin accumulate within the cells.[10] Widespread degenerative changes ensue; in the trabecular meshwork these changes include sclerosis and obliteration of the intertrabecular spaces. Thus, in contrast to hemolytic glaucoma, in which aqueous outflow is blocked by cells and debris entrapped in the meshwork, the glaucoma associated with hemosiderosis is due to degenerative changes in the meshwork itself.

Clinically, hemosiderotic glaucoma is distinguished from hemolytic glaucoma by its chronic course, prolonged history of recurrent bleeding, and by the presence of other signs of ocular hemosiderosis. These include retinal degeneration, cataract, iris discoloration, and iron-staining of the cornea.

Because eyes with vitreous hemorrhages are susceptible to both hemolytic glaucoma and hemosiderosis, the two conditions may occasionally be superimposed in the same eye. Such a concurrence is suggested by several histologic reports of ocular hemosiderosis, in which the trabecular meshwork was sclerosed and obliterated, but also was infiltrated by iron-containing macrophages.[11-13]

Neovascular glaucoma, the second condition from which hemolytic glaucoma must be differentiated, is characterized by rubeosis, a network of newly formed blood vessels proliferating over the anterior surface of the iris and onto the trabecular meshwork. Associated with the new vessels is a fine fibrous membrane that obstructs aqueous outflow and ultimately contracts, leading to the formation of peripheral anterior synechiae. Rubeosis is typically a complication of a retinal vaso-occlusive disorder, usually a central retinal vein thrombosis or severe diabetic retinopathy. Because the underlying retinal vascular disease may be associated with vitreous hemorrhage, and because hyphemas not infrequently accompany rubeosis, neovascular glaucoma has been called hemorrhagic glaucoma. The adjective hemorrhagic should be discarded: it erroneously implies a role for hemorrhage in the etiology of the glaucoma, and it can easily be confused with hemolytic.

A tentative diagnosis of hemolytic glaucoma may be made if the following clinical criteria are present: (1) elevated intraocular pressure; (2) antecedent large intraocular hemorrhage; (3) open angle by gonioscopy; (4) reddish or reddish-brown appearance of the trabecular meshwork; (5) no rubeosis on the iris or in the chamber angle; and (6) red blood cells in the aqueous humor (some of these may be true red blood cells; others may be hemoglobin-stuffed macrophages).

Because of its etiology, the disease is typically unilateral. The glaucoma often begins abruptly, with symptoms of pain, congestion, and corneal edema, but may be insidious in onset, as in our third patient. It may later become chronic, especially if the vitreous hemorrhage is recurrent, and can ultimately produce glaucomatous atrophy of the optic disk. It may also fluctuate in severity, making monitoring of medical control difficult.

Two adjuncts to diagnosis have helped us. The first is ultrasonography which assists in the diagnosis of vitreous hemorrhage when cataract is present and which may also detect an underlying retinal detachment. The second is examination of aspirated aqueous humor for pigment-containing macrophages.[14] A cytopathology laboratory with experience in examining small aliquots of fluids (such as cerebrospinal fluid) for cellular morphology greatly assists ophthalmologists. The aqueous samples must be processed immediately and should be filtered with great care to avoid rupturing of the cells.

Although the outcome of our cases has not been totally satisfactory in all instances, we have learned from them and recommend the following plan of management. We believe standard medical treatment for glaucoma should be attempted first, including the use of miotics, epinephrine, carbonic anhydrase inhibitors, and hyperosmotic agents. If this treatment is successful, the patient must be followed at frequent intervals, so that exacerbations can be detected and managed in time, or so that medications can be decreased if the process resolves.

If nonspecific therapy is ineffective, a more specific approach should be tried. When the underlying hemorrhage is probably nonrecurrent or is a hyphema, one or more anterior chamber washouts are indicated, accomplished through a beveled, wide paracentesis incision in clear cornea near the corneoscleral limbus. Aqueous humor should be aspirated and sent to the cytopathology laboratory for confirmation of the diagnosis, and the anterior chamber should be gently washed until the aqueous humor seems clear. This procedure can be repeated easily when necessary through the same unsutured incision.

If the vitreous hemorrhage is recurrent and is associated with hemolytic glaucoma, a subtotal vitrectomy is indicated, using one of the new motorized vitreous cutting and sucking instruments. Removal of the vitreous hemorrhage eliminates the cause of the glaucoma and may reveal a treatable source of the hemorrhage.

Summary

The clinical manifestations of hemolytic glaucoma in five patients showed that the glaucoma began after a large intraocular hemorrhage. Gonioscopy revealed open angles in the anterior chamber and reddish-brown pigment covering the trabecular meshwork. Numerous red-tinted blood cells were floating in the aqueous humor; some of these were macrophages found by cytologic examination to contain golden-brown pigment granules.

The presumed cause of hemolytic glaucoma is obstruction of the trabecular meshwork by fragments of hemolyzed red blood cells and hemoglobin-laden macrophages. Two patients, whose intraocular pressures were not decreased with medication, improved remarkably after irrigation of hemolytic debris from the anterior chamber.

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Ophthalmic miniature

Considering how common illness is, how tremendous the spiritual change that it brings, how astonishing, when the lights of health go down, the undiscovered countries that are then disclosed, what wastes and deserts of the soul a slight attack of influenza brings to view, what precipices and lawns sprinkled with bright flowers a little rise of temperature reveals, what ancient and obdurate oaks are uprooted in us by the act of sickness, how we go down into the pit of death and feel the waters of annihilation close above our heads and wake thinking to find ourselves in the presence of the angels and the harpers when we have a tooth out and come to the surface in the dentist's arm-chair and confuse his "Rinse the mouth—rinse the mouth" with the greeting of the Deity stooping from the floor of Heaven to welcome us—when we think of this, as we are so frequently forced to think of it, it becomes strange indeed that illness has not taken its place with love and battle and jealousy among the prime themes of literature.

Virginia Woolf, *The Moment and Other Essays*
New York, Harcourt Brace and Co., 1948

SURGICAL LANDMARKS IN TRABECULAR SURGERY

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For the past decade, there has been a gradual increase in the use of so-called trabecular surgery in the management of certain types of glaucoma.[1-3] The transition toward this type of surgery has been aided greatly by the increasing availability and use of the operating microscope, and the concept that the surgical attack should be directed at the exact locus of this disorder.[4] It follows, then, that the use of the operating microscope is mandatory in performing surgery in this area because of the need to locate precisely the anatomic landmarks.[5] The difficulty that such localization sometimes poses, and the mystique surrounding this type of surgery, have dissuaded many from attempting to develop skill in the performance of any one of a family of operations—often, but inappropriately, termed "trabeculectomy"—that have proved to be successful and are relatively complication-free types of glaucoma surgery.

SUBJECTS AND METHODS

Thirty-one of 35 patients included in this study were scheduled for surgery because of uncontrollable adult open-angle glaucoma with progressive visual field loss. The remaining four had uncontrolled chronic angle-closure glaucoma, for which iridectomies had been performed at least two years previously to relieve the angle-closure component. Although these procedures have been performed in congenital glaucomas, juvenile glaucomas, secondary glaucomas, neovascular glaucomas, and aphakic glaucomas, we considered only the aforementioned glaucoma types for this study. Success was defined as intraocular pressure less than 18 mm Hg by applanation tonometry without medication for at least two years.

Forty eyes were studied. A 3 × 5-mm scleral flap, 0.5 mm thick, was fashioned in all cases, and then the surgical technique varied in one of three ways (Fig. 1). In 16 eyes in Group 1, Schlemm's canal was identified, entered, and a block of tissue 1 × 3 mm, whose posterior border included Schlemm's canal, was excised (Fig. 2). In 16 eyes in Group 2, the suprachoroidal space was entered posterior to the scleral spur and a block of tissue 3 × 3 mm including scleral spur and Schlemm's canal was excised (Fig. 3). In Group 3, the chamber was entered at the anterior margin of the lamellar flap and a 1.5 × 3-mm segment of posterior lamellar scleral tissue was excised in an anteroposterior direction (Fig. 4). No at-

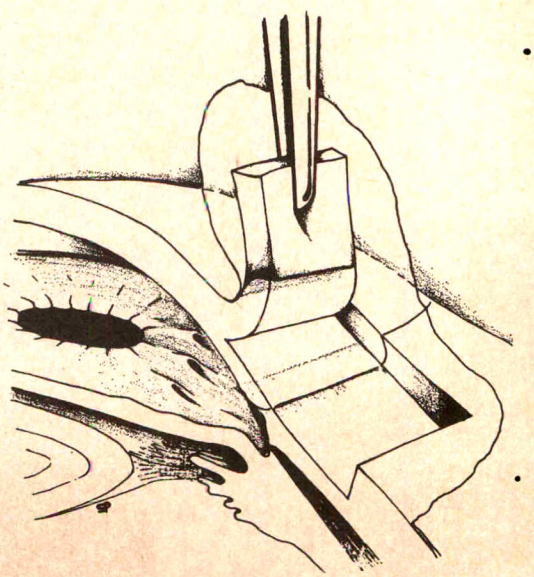


Fig. 1 (Galin, Boniuk, and Robbins). Standard initial lamellar scleral flap for performing trabeculectomies.

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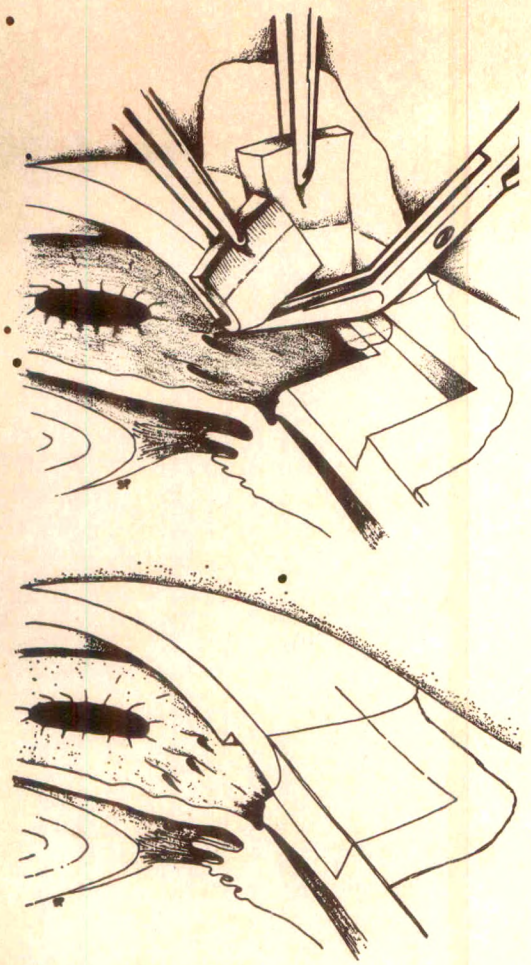


Fig. 2 (Galin, Boniuk, and Robbins). Top, Excision of posterior scleral layer, anterior to scleral spur, contains Schlemm's canal and trabecular tissue. Bottom, Appearance of eye at end of procedure.

tempt was made to reach the scleral spur in this latter method that essentially was a lamellar posterior lip sclerectomy under a scleral flap.

All available tissue was embedded in paraffin and serial sections were cut and stained either with hematoxylin and eosin or with PAS stains. All sections were evaluated particularly for the presence of identifiable landmarks, including Schlemm's canal and trabecular tissue.

Results

The Table lists the results of surgery in the three groups, as well as certain long-term clinical features of the operated eyes. Success was achieved in an equal percentage in all groups. The incidence of polycystic bleb formation, however, was greatest in Group 3 (the posterior lip sclerectomy operation) while the lowest levels of intraocular pressure occurred in Group 2. No trabecular meshwork was seen in any of the specimens of Group 3 but it was universally present in the specimens of Groups 1 and 2 (Fig. 5). Surgical correlation with the histologic specimens of Group 3 clearly demon-



Fig. 3 (Galin, Boniuk, and Robbins). Top, Excision of posterior scleral layer posterior to scleral spur contains scleral spur, Schlemm's canal, and trabecular meshwork. Bottom, Appearance of eye at end of procedure.

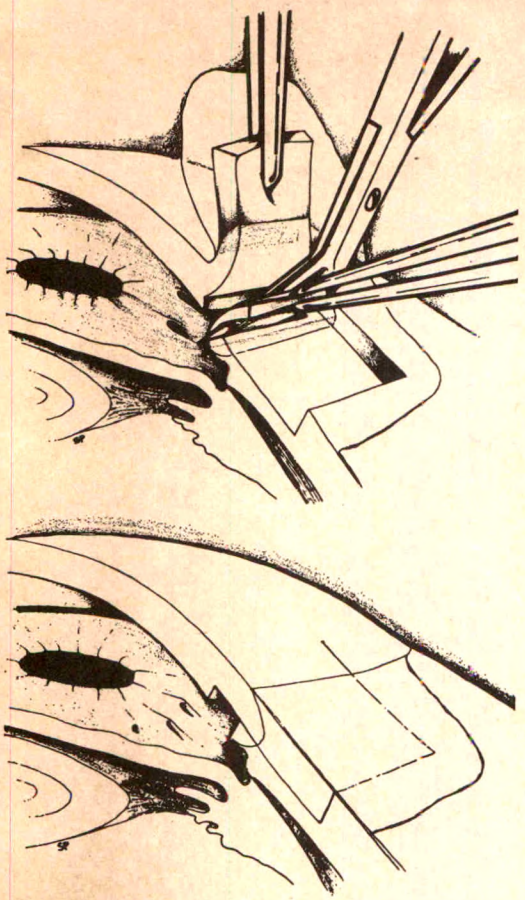


Fig. 4 (Galin, Boniuk, and Robbins). A lamellar posterior lip sclerectomy performed in an antero-posterior direction (top).

strated that success can be achieved without the presence of trabecular tissue.

Discussion

This study indicates that the surgical results of the operations termed trabeculectomy are, indeed, excellent. Further, it does not appear that the localization of certain angle landmarks, such as Schlemm's canal, enhance the clinical success of the procedure. Nor, apparently, does it matter that trabecular tissue or Schlemm's canal be excised for this operation to be successful.[6] On the contrary, in those cases in which an attempt was made specifically not to excise these tissues, which was proven histologically, clinical success was equally evident.

The procedures described here are really three different operations, although each has been termed trabeculectomy. They are obviously surgically different, and have different long-term results. The operation in Group 1, appropriately termed "canaliculo-trabeculectomy under a scleral flap," is surgically the most difficult. This operation requires more expertise with the operating microscope than what is necessary to perform an adequate sclerectomy under a scleral flap. It is essential to find Schlemm's canal in performing trabeculotomies for congenital

TABLE

Results of 3 different types of trabeculectomy procedures

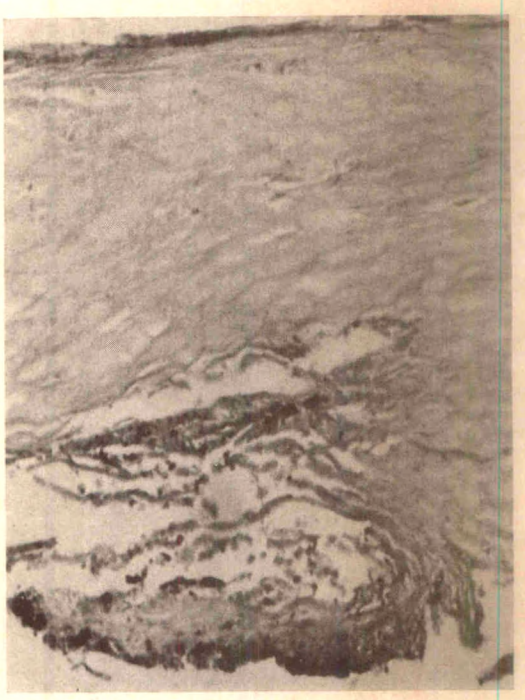
	Intraocular Pressures, mm Hg*					Bleb			
	7–10	11–14	15–18	19–22	23–26	Nothing Visible	Visible on Slit Lamp	Grossly Visible	Polycystic
Group 1 (Canaliculo-trabeculectomy)		4	9	2	1	4	4	7	1
Group 2 (Canaliculo-trabeculectomy with cyclodialysis)	2	8	6			3	5	6	2
Group 3 (Lamellar posterior lip sclerectomy)		2	4	1	1		1	5	2

* No medication.

glaucoma and adult open-angle glaucoma (a procedure with poor results in our hands) and perhaps in attempting to clarify how trabeculotomies work.[7] For surgical training, then, it might be fruitful to localize Schlemm's canal while doing sclerectomies under a scleral flap. However, to achieve a surgical cure, the localization of Schlemm's canal is unnecessary. This procedure results in a formed chamber at the conclusion of surgery, a rather diffuse, nonpolycystic bleb, and intraocular pressures usually between 14 and 22 mm Hg.

The operation in Group 2, termed "canaliculotrabeculectomy under a scleral flap with cyclodialysis," is an excellent standard glaucoma operation and is the operation of choice in complex cases, since this procedure can easily be performed even when landmarks as gross as the corneoscleral limbus are





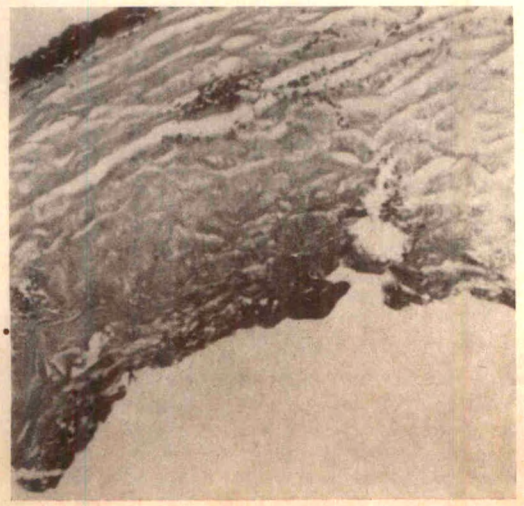


Fig. 5 (Galin, Boniuk, and Robbins). Top left, Area of trabecular meshwork attached to scleral lamella (PAS, ×40). Top right, En bloc excision of lamellar layer of sclera from posterior to the scleral spur into cornea includes entire angle area (hematoxylin and eosin, ×10). Left, Scleral and corneal fragment. No angle tissue is present (hematoxylin and eosin, ×10).

totally obliterated. Since the posterior lamellar flap is always attached to the scleral spur, a cyclodialysis is automatically carried out in order to enter the anterior chamber. Excision of this posterior lamella from behind the scleral spur, anterior to the point of entrance into the chamber, assures that the posterior flap contains Schlemm's canal and trabecular tissue. In our experience, this operation results in intraocular pressures lower than in Groups 1 and 3, in the range of 10 to 18 mm Hg. The anterior chamber remains formed and polycystic bleb formation is uncommon, but the inflammatory response to surgery, though mild, is greater than in Groups 1 and 3.[8] In general, the more common fistulizing operations with sclerostomies covered only by conjunctiva result in both short- and long-term intraocular pressures less than any trabeculectomy procedure, in shallow to absent anterior chambers the first few days after surgery, and in much posterior synechiae formation.[9] It is possible that the profound postoperative hypotony results in the acceleration of already existing lens change. Whether or not trabeculectomy procedures do the same remains to be demonstrated. Group 2 operations though come closest to the pressure ranges obtained with standard fistulizing operations.

The operation in Group 3, termed a "posterior lamellar sclerectomy," is almost the same as the standard posterior lip sclerectomy under a conjunctival flap except for its performance under a scleral flap. It is an operation familiar to most eye surgeons, yields excellent results, and does not require extraordinary microscopic expertise. Its major drawback appears to be more bleb formation than the other two operations produced but less than standard fistulizing operations produced.

Although there are a variety of explanations as to how trabeculectomies work, most evidence is that they are simply modified fistulizing operations.[10] Standard through-and-through sclerostomies under conjunctival flaps permit the exit of most of the bulk flow of aqueous humor from the sclerostomy until a variety of factors tend to reduce and redirect this flow. As a consequence, chambers are shallow to absent the first few days and subconjunctival as well as conjunctival alterations leading to appreciable polycystic bleb formation frequently occur. With trabeculectomies, the anterior lamellar flap tamponades the sclerostomy, resulting in increased postoperative intraocular pressures, formed chambers, and slower diffusion of aqueous humor. It is probably this latter aspect that reduces local polycystic bleb formation. The surgeon has some control with respect to controlling aqueous flow in trabeculectomy procedures by the thickness and how tight the anterior scleral flap is sutured. Rather loose reapproximation results in greater bleb formation, decreased intraocular pressures and, probably, greater success than a watertight closure.

We do not intend to discourage the use of the operating microscope, but to put straight the false sophistication that is developing concerning surgery carried out with microscopic assistance. Ocular surgery with such assistance is simply surgery performed with helpful illumination and good magnification. It is not surgery done on a microscopic level. These are still procedures in which the surgeon is by far the most important component.

Summary

Clinical and histologic studies in 40 eyes of 35 patients with chronic open-angle glaucoma or chronic angle-closure glaucoma operated by various types of "trabeculectomies" were assessed to evaluate whether success was correlated with the surgical approach or with the presence of trabecular tissue in the pathologic specimen. It was clearly demonstrated that it is not necessary to localize or enter Schlemm's canal in order to perform successful trabeculectomies; it is not necessary to operate posterior to the scleral spur; and it is not necessary to excise

either Schlemm's canal or trabecular tissue to achieve success. In essence, trabeculectomies primarily function as fistulizing operations carried out under scleral flaps substituting a scleral-conjunctival barrier to aqueous flow rather than the conjunctival barrier alone provided by standard glaucoma operations. This greater obstruction explains the absence of shallow chambers, the reduced incidence of polycystic bleb formation and, perhaps, an avoidance of long-term complications that often result from these two factors.

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EFFECT OF RETINAL DETACHMENT SURGERY ON THE COURSE OF PREEXISTING OPEN-ANGLE GLAUCOMA

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The prevalence of open-angle glaucoma in patients with retinal detachment is high and, according to various authors, it varies between 12 and 17%.[1-3] Surprisingly, only a few authors[4-6] have reported on the intraocular pressure in glaucomatous eyes after surgery for retinal detachment and none have described the follow-up with regard to the glaucomatous state. We describe the effect of retinal detachment surgery on the clinical course of open-angle glaucoma in 12 eyes over 5½ years.

MATERIAL AND METHODS

Between January 1969 and December 1973, 12 eyes of 12 patients with chronic simple glaucoma were operated on for retinal detachment. Chronic simple glaucoma was diagnosed before the appearance of retinal detachment in six patients, and the diagnosis in the remaining six patients was established when the patients were admitted to the hospital because of retinal detachment. The diagnosis of open-angle glaucoma was based on the finding of open angles in all eyes and on some or all of the following features found in one or in both eyes of the 12 cases: intraocular pressures of 26 mm Hg or more, initial pressure/facility of outflow (Po/C) over 100 on electrotonography, glaucomatous disk cupping, and glaucomatous field defects. After retinal surgery the retina reattached in all 12 cases. The follow-up period since retinal reattachment was one to 5.5 years. We took repeated measurements of the intraocular pressure with the Goldmann applanation tonometer attached to the 900 Haag-Streit slit lamp, gonioscopy and perimetry were performed, and both optic disks were examined with the contact lens. Electrotonography was performed after retinal reattachment on both eyes of ten patients at the end of the follow-up period.

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RESULTS

There were nine men and three women, ranging in age from 47 to 67 years. Retinal detachment was complete in one patient, in two it involved three quadrants, in seven it included two quadrants, and in two patients it involved one quadrant (Table 1).

In all 12 eyes light diathermy through a full-thickness sclera was used to seal the retinal breaks and fluid was tapped through a scleral incision. In nine eyes a 2-mm wide encircling silicone band was used and in seven eyes a silicone episcleral implant was placed under the encircling band. In the nine cases the band was stretched and shortened by 15 to 20% of its length when placed around the globe before we tapped subretinal fluid. In two patients (Cases 10 and 11), an extensive lamellar scleral resection was performed. In Case 12 an episcleral implant of silicone sponge was used, but this partially extruded one month later and was removed.

Table 2 summarizes the more important data concerning the glaucomatous state of both eyes of each of the 12 patients before and after surgery for retinal detachment as well as the time lapse since retinal surgery. In the 12 fellow eyes without retinal detachment, the diagnosis of open-angle glaucoma was based on increased intraocular pressure, 26 mm Hg or more, that required conservative treatment in 11 eyes and a filtering procedure in one eye. The electrotonographic tracings were typical for open-angle glaucoma in ten of the fellow eyes on which it was performed. All the angles were wide open. There was glaucomatous excavation with or without glaucomatous field defects in four

TABLE 1

DATA ON EXTENT OF RETINAL DETACHMENT AND TYPE OF OPERATION PERFORMED

Case No., Age, yrs, Sex	Extent of Retinal Detachment	Type of Operation Performed
1, 56, F	Upper half	Encircling silicone buckle and episcleral silicone implant
2, 48, F	Temporal half	Encircling silicone buckle and episcleral silicone implant
3, 67, M	Upper temporal quadrant	Encircling silicone buckle and episcleral silicone implant
4, 62, M	Upper half	Encircling silicone buckle and episcleral silicone implant
5, 59, M	3 quadrants	Encircling silicone buckle and episcleral silicone implant
6, 47, M	Upper half	Encircling silicone buckle and episcleral silicone implant
7, 65, M	Temporal half	Encircling silicone buckle and episcleral silicone implant
8, 66, M	Upper half	Encircling silicone buckle
9, 50, M	3 quadrants	Encircling silicone buckle
10, 63, F	Total	Extensive lamellar scleral resection
11, 65, M	Lower half	Extensive lamellar scleral resection
12, 61, M	Upper temporal quadrant	Localized silicone sponge episcleral implant

of the fellow eyes, one of which was blind from glaucoma.

Of the 12 eyes with retinal detachment, glaucoma had been diagnosed in six cases, seven months to six years before retinal detachment occurred. These six eyes were receiving pilocarpine treatment when the detachment occurred, and without miotics the intraocular pressure had reached 34 to 40 mm Hg. In four of these six eyes there was glaucomatous excavation with or without glaucomatous field defects. The electrotonographic tracings after retinal surgery were abnormal in four of these eyes. In the remaining six eyes glaucoma was diagnosed after retinal detachment occurred. The diagnoses were based on finding open-angle glaucoma in the fellow eyes, wide open angles, and abnormal electrotonographic tracings. Glaucomatous excavation, glaucomatous field

TABLE 2

DATA CONCERNING THE GLAUCOMATOUS STATE IN THE EYES WITH RETINAL DETACHMENT AND IN THE FELLOW EYES*

Case No.	Time lapse (yrs) Between Diagnosis of Glaucoma and RD	Highest IOP (mm Hg) Before RD	IOP (mm Hg) at RD	Cup/Disk Ratio, State of Disk		Visual Fields		ETG, Po/C†		Range of IOP (mm Hg) After RD Operation		Antiglaucomatous Treatment After RD Surgery		Follow-up (yrs) Since RD Surgery
				Eye with RD	Fellow Eye	Eye with RD	Fellow Eye	After RD Surgery	Fellow Eye	Eye with RD	Fellow Eye	Eye with RD	Fellow Eye	
1	0	—	15	0.7, kinking	0.7, kinking	Nasal step	Normal	12/0.10	20/0.17	8–10	19–37	0	+	4.5
2	0	—	8	0.7	0.5	Nasal step	Normal	11/0.08	21/0.09	10–15	19–29	0	+	4.5
3	0	—	24	0.3, kinking	0.3, kinking	Normal	Nasal step	18/0.06	24/0.16	12–19	17–37	0	+	4.5
4	6	37	12	0.2	0.2	Normal	Normal	18/0.08	25/0.09	14–22	17–41	0	+	1
5	3	37		0.8	0.3	Concentric 5–20°	Normal	19/0.10	19/0.07	18–21	18–34	0	+	5.5
6	4 mos	?	12	0.2	0 2	Normal	Normal	14/0.12	36/0.12	5–17	17–40	0	+	3.5
7	5	34		0.5, kinking	0.5, kinking	Normal	Nasal step	12/0.04	19/0.10	12–20 (28 once)	15–30	0	+	1
8	0	—	17	0.2	0.2	Normal	Normal	12/0.11	23/0.14	16–21	16–27	0	+	4.5
9	2	40		1.0, atrophy	0.9, atrophy	Tubular 5°	Tubular 10–15°	—	—	10–16	22–40	0	+ Surgery	2.5
10	0	—		0.2	0.2	Bjerrum's scotoma	Normal	9/0.15	19/0.06	14–18	20–30	0	+	2
11	0	—	27	0	0	Normal	Normal	—	—	8–17	13–26	0	+	5.5
12	7 mos	34	9	0.5, kinking	0.3	Nasal step	Normal	25/0.04	17/0.08	17–27	17–26	+	+	1.25

* RD indicates retinal detachment; IOP, intraocular pressure; ETG, electrotonography; Po/C, initial pressure outflow facility.
† Values recorded are those of the last ETG performed at the end of the follow-up period just before publication.

defect, or both, were found in four of these six eyes. The diagnosis of glaucoma was doubtful in Case 11 since electrotonography was not performed. Moreover, if typical visual field defects or glaucomatous excavation of the optic disk in at least one eye are essential features for the diagnosis of open-angle glaucoma and increased intraocular pressure and electrotonographic tracings are ignored, then the diagnoses in Cases 4, 6, and 8 are also doubtful. Nonetheless, in these three cases the electrotonographic tracings were abnormal and the highest intraocular pressure in one of the two eyes of each of these three cases was 41, 40, and 27 mm Hg, respectively.

At the time of retinal detachment, the intraocular pressure was measured in eight of the 12 eyes and was low, 8 to 12 mm Hg, in four of them, normal in two, and elevated in the remaining two eyes. Following retinal surgery antiglaucomatous treatment was stopped. Intraocular pressures in ten of the operated eyes ranged from 5 to 21 mm Hg. In one eye (Case 7), there was an occasional increase in pressure to 28 mm Hg, but this became hypotonic as soon as treatment was reestablished. In Case 12, a month after removal of a silicone sponge implant, intraocular pressure gradually increased to 27 mm Hg.

The follow-up period since retinal surgery was one to 5½ years. During this period antiglaucomatous treatment had to be resumed in one patient (Case 12). No deterioration of the visual fields occurred, nor did the appearance of the optic disk change in any of the 12 eyes operated on for retinal detachment.

Discussion

In the 12 eyes with chronic simple glaucoma that underwent surgery for retinal detachment, intraocular pressure remained low after reattachment of the retina in 11 eyes for one to 5½ years. No antiglaucomatous treatment has been required and no further deterioration in the state of the optic disks or of the visual fields has occurred in any of these eyes. An encircling silicone band, stretched and shortened by 15 to 20% of its length when placed around the globe, was used in nine eyes and an extensive lamellar scleral resection was performed on two eyes. Since the facility of outflow remained low, the hypotension that ensued after the operation must have been due to hyposecretion of the ciliary body. Ophthalmoscopically, a high buckle can still be seen in all these eyes and presumably this causes kinking and narrowing of the long posterior ciliary arteries that could, in turn, account for the prolonged hyposecretion of the ciliary body.

The superficial scleral diathermy performed in the 11 eyes probably did not contribute much to the ciliary hyposecretion since it was never placed over the long posterior ciliary arteries or over the ciliary body itself. In the eye that was placed on miotic treatment after the reattachment of the retina, superficial scleral diathermy was performed but no encircling procedure was used.

Assuming that encircling buckling procedures lead to hyposecretion of the ciliary body, one would expect decreased intraocular pressure, even in eyes without glaucoma, after similar surgery. Syrdalen[7] reported on the intraocular pressure after surgery for retinal detachment in 55 eyes without glaucoma. In 42 eyes, an encircling buckling operation with a silicone rubber band was used and in 13 eyes only a local buckle was employed. In both groups, intraocular pressure in the operated eye was lower than that found in the fellow eye. The effect was more marked and more prolonged in the 42 eyes that underwent an encircling procedure.

We found only three published reports in which the intraocular pressure of glaucomatous eyes was mentioned after surgery for retinal detachment. Sebestyen, Schepens, and Rosenthal[4] reported on the gonioscopic findings and the intraocular pressure in 160 eyes that underwent an encircling procedure with a polyethylene tube because of retinal detachment. Two of these patients had had

open-angle glaucoma and in one of them, antiglaucomatous treatment was stopped a year after retinal surgery because of normal intraocular pressure. In the second patient, intraocular pressure remained elevated. Sarin, Chessen, and McDonald[5] reported a single case of unspecified glaucoma in which the intraocular pressure was decreased three months after surgery for retinal detachment and in which an encircling polyethylene tube was used. Lawton-Smith[6] reported on six eyes operated on for retinal detachment and two eyes operated for retinal tears, all with chronic simple glaucoma. Scleral diathermy, localized buckles, lamellar scleral resections, and encircling procedures with a polyethylene tube were used. Apparently, antiglaucomatous treatment was stopped in only one of these eyes after retinal surgery. Therefore, it seems retinal detachment or various surgical procedures for reattachment of the retina do not lead to lasting hypotony in most cases of open-angle glaucoma.

Apart from these three reports dealing with primary glaucoma and retinal detachment, Schwartz[8] reported on unilateral elevated intraocular pressure secondary to retinal detachment, mostly of traumatic origin, that returned to normal after reattachment of the retina. Uveitis was considered as an important contributing factor. With the reattachment of the retina the facility of outflow that was reduced returned to normal. Sebestyen, Schepens, and Rosenthal[4] reported on the occurrence of glaucoma in 16 of 160 eyes after retinal detachment surgery. Trabecular pigmentation and closure of the anterior chamber angles by anterior synechiae occurred in 19 eyes. In all 160 eyes, an encircling procedure with a polyethylene tube was done.

A measured shortening of an encircling silicone band seems to have a sustained effect on decreasing intraocular pressure in patients with primary open-angle glaucoma, and antiglaucomatous treatment can be discontinued for long periods of time without further deterioration of the visual fields. This may constitute a new approach to the surgery of open-angle glaucoma, not necessarily limited to cases of retinal detachment, in which hyposecretion of the ciliary body is desired.

Summary

In 11 of 12 eyes with chronic simple glaucoma after surgery for retinal detachment, intraocular pressures were decreased for one to 5½ years without any antiglaucomatous treatment. No further deterioration in the state of the optic disks or the visual fields occurred in any of these eyes. In all 12 fellow eyes antiglaucomatous treatment is still being administered.

The operation employed in nine of the 11 cases consisted of an encircling silicone rubber band shortened by 15 to 20% of its length when placed around the eyeball before tapping subretinal fluid. An episcleral silicone implant was placed under the encircling band in seven of these eyes. Kinking and possibly narrowing of the long posterior ciliary arteries by the encircling silicone band probably caused the ciliary hyposecretion and the resultant hypotony.

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COMPARATIVE PHARMACOLOGIC EFFECTS OF PILOCARPINE ADMINISTERED TO NORMAL SUBJECTS BY EYEDROPS OR BY OCULAR THERAPEUTIC SYSTEMS

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Ocular therapeutic systems delivering 20 or 40 μg/hour of pilocarpine to the eye at an essentially constant rate control intraocular pressure without the side effects and inconvenience of conventional eyedrop therapy.[1-6] The two elliptically shaped systems (Ocusert Pilo-20 and Pilo-40) have a pilocarpine core reservoir surrounded by a rate-controlling ethylene/vinyl acetate copolymer membrane (Fig. 1). These systems are 0.3 and 0.5 mm thick, respectively, and each is approximately 5.5 mm wide and 13 mm long. Placed in the conjunctival cul-de-sac, they release 0.48 or 0.96 mg/day of pilocarpine for seven days. Eyedrop therapy of one 0.05-ml drop of a 1, 2, or 4% solution, four times daily, provides 2 to 8 mg of pilocarpine per day.

The ocular therapeutic system avoids the "pulse" effects of eyedrops. High tissue concentrations occur transiently in rabbit eyes immediately after eyedrop instillation.[7] These appear necessary to provide a medication level in the target tissues that maintain adequate therapeutic activity between doses.

We summarize pilocarpine's ocular effects in normal volunteers who received the drug in 1, 2, and 4% ophthalmic drops and from Pilo-20 and Pilo-40 systems.

SUBJECTS AND METHODS

The six subjects of the study (Table 1) had normal intraocular pressures and visual acuity and no ocular pathology, and gave informed consent. For orientation, each subject received a drop of 1% pilocarpine in one eye and a 20 μg/hour ocular therapeutic system in the fellow eye after instruction on its use. During the next two hours repeated measurements of intraocular pressures, visual acuity, miosis, and myopia were made. The actual investigation started one week later.

The intraocular pressures reported here are the mean of three consecutive tonometric measurements of each eye. The mean values were not significantly different from the medians. Visual acuity was measured with the refracting eye chart with letter charts at a distance of 20 feet. The refractive change was determined by fogging with plus lenses to reduce visual acuity to 20/70 and then determining the number of diopters needed to restore vision to baseline acuity (20/16 or 20/20). Miotic effects were determined from 35-mm color slides of the eye taken at a fixed standard distance after 15 seconds of dark exposure. Measurements of pupil-to-iris ratio were made subsequently from rear-screen projection of the slides.

On Tuesday morning, after a one-week period of measurements made during use of placebo drops or placebo therapeutic systems, we began studies to compare the effects of pilocarpine delivered by eyedrops to one eye and by the ocular therapeutic system to the fellow eye. Each subject was studied during successive weeks according to the regimens

TABLE 1

CHARACTERIZATION OF VOLUNTEERS

Age, Sex, Race	Color of Eyes
32, M, White	Brown
35, M, Black	Brown
35, F, White	Green
41, F, White	Blue
33, F, White	Blue
38, M, White	Blue

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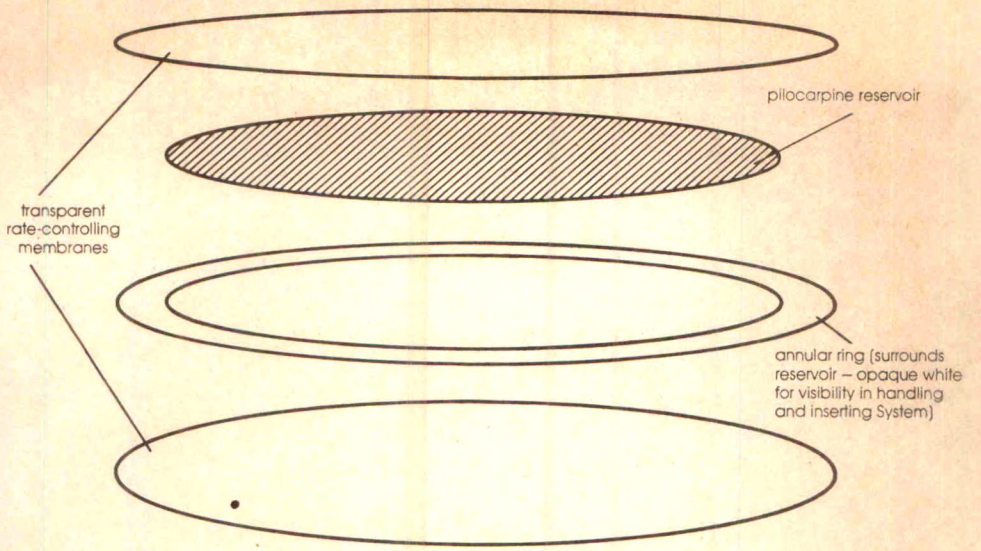


Fig. 1 (Place and associates). Diagram of membrane-controlled ocular therapeutic system.

shown in Table 2 and the measurement schedule shown in Table 3. We measured intraocular pressure, visual acuity, refractive changes, and miosis in both eyes before and after eyedrop instillation in one as shown in Table 3. Examinations were made on Wednesdays, Fridays, and Mondays (days 2, 4, and 7). Volunteers were examined at two of three weekly sessions, so that the six subjects were observed simultaneously.

TABLE 2

REGIMEN* FOR COMPARING PHARMACOLOGIC EFFECTS OF PILOCARPINE EYEDROPS IN ONE EYE WITH PILOCARPINE THERAPEUTIC SYSTEM IN FELLOW EYE

Week	Regimen	
	Therapeutic System, Placed Once Per Wk	Eyedrops, Three Times Daily†
1	Placebo unit	Polyvinyl alcohol
2	Pilo-20	1% pilocrapine
3	Pilo-20	2% pilocarpine
4	Pilo-40	4% pilocarpine
5	Pilo-20 placed in both eyes once/wk for 7-day use	

* Choice of right or left eye for drops or therapeutic system was randomized until week 5.
† Administered at 8 AM, 2, and 8 PM.

RESULTS

Volunteers wearing a placebo unit in one eye and receiving placebo eyedrops, three times daily, in the other for one week had essentially the same intraocular pressures, visual acuity, refractive errors, and pupil-to-iris ratio in both eyes. There was no ocular irritation, and the subjects usually had no awareness of the ocular therapeutic system in their eye.

Average intraocular pressures and standard deviations for the group are summarized in Table 3. There were no significant differences between intraocular pressures, refractive errors, visual acuity, or miosis measured at corresponding times on

TABLE 3

INTRAOCULAR PRESSURES* OF NORMAL VOLUNTEERS RECEIVING PILOCARPINE EYEDROPS† AND OCULAR THERAPEUTIC SYSTEMS

Hour	Week 1		Week 2		Week 3		Week 4		Week 5	
	Placebo	Polyvinyl Alcohol	Pilo-20	1% Pilocarpine Eyedrops	Pilo-20	2% Pilocarpine Eyedrops	Pilo-40	4% Pilocarpine Eyedrops	Pilo-20	Pilo-20
8‡	16.16±2.19	16.14±2.35	15.22±2.43	15 33±2.39	15.47±2.30	15.22±2.35	14.36±2.71	14.94±2.70	15.04±3.15	14.87±2.12
8:30	17.17±2.03	17.22±2.10	16.06±2.06	15.81±1.96	15.83±1.84	15.33±2.83	15.17±2.38	15.00±2.06	15.04±2.19	14.87±3.12
9	16.11±1.61	16.08±1.36	16.25±2.22	15.81±2.12	16.08±1.89	15.06±2.27	15.28±2.44	14.83±2.65	15.46±1.88	15.00±1.94
10	16.50±2.03	16.94±1.86	15.56±2.19	15.53±1.98	15.39±1.76	15.39±1.94	15.33±2.49	14.81±2.12	16.21±2.89	15.58±2.65
14‡	15.44±2.65	14.89±2.09	14.44±1.81	14.94±1.94	14.56±1.67	14.22±1.42	14.81±2.44	14.89±2.54	15.21±2.12	14.37±1.77
14:30	14.97±2.84	15.50±2.52	14.47±1.99	13.81±1.71	14.69±2.13	13.06±2.05	14.58±2.28	13.36±2.32	15.17±1.39	14.87±1.70
15	15.31±2.89	15.25±1.74	14.56±1.89	13.94±1.64	14.36±2.23	12.72±1.55	15.00±2.57	13.81±2.70	14.75±2.05	14.62±2.10
16	15.36±3.29	15.64±3.25	14.36±1.84	14.50±1.54	14.25±1.76	13.78±1.92	14.67±2.24	14.31±2.01	15.62±2.70	14.71±2.27
20‡	14.08±2.11	14.17±1.96	13.17±1.49	13.11±1.42	13.75±2.69	13.28±1.82	13.11±2.04	12.75±1.93	14.04±3.08	13.29±2.35
20:30	13.64±2.06	13.69±1.45	14.00±2.22	12.94±1.98	13.56±2.15	12.17±1.35	13.28±1.96	12.14±1.16	13.62±2.65	12.67±1.63
21	13.31±1.67	13.47±0.98	13.31±1.95	12.92±1.92	13.09±2.00	12.03±1.68	13.47±2.01	12.33±1.33	13.12±2.40	12.79±1.59
22	13.44±1.93	13.67±1.84	13.11±2.29	12.89±2.09	12.86±1.74	12.08±1.58	12.67±1.62	11.92±1.39	13.12±2.79	12.87±2.25

* Each number represents the average of three measurements in millimeters of mercury made on days 2, 4, and 7 of each week, and the standard deviation.
† Times of eyedrop instillations. Measurements were made immediately before instillation.
‡ Standard deviation.

days 2, 4, and 7 of therapy for a given therapy or placebo.

Both pilocarpine eyedrops and ocular therapeutic systems decreased normal intraocular pressure by 0.5 to 2.0 mm Hg from the pressures measured at corresponding times during placebo medication.

Pilocarpine eyedrops produced large and widely varying effects on myopia, visual acuity, and miosis. In contrast, visual changes produced by the Pilo-20 and Pilo-40 systems were small and relatively constant.

Visual acuity—We measured visual acuity by the Snellen chart (Fig. 2). Volunteers wearing a Pilo-20 system had visual acuities not different significantly from normal or from those obtained during placebo use. The visual acuities of the volunteers receiving 1% pilocarpine eyedrops decreased from 20/20 pretherapy to less than 20/100, one half hour after therapy, and returned to normal two hours later (Fig. 2, left). The results with 2% pilocarpine eyedrops were similar.

The Pilo-40 system produced a fairly constant decrease in visual acuity to about 20/30. The subjects' visual acuity was 20/16 before they received 4% pilocarpine eyedrops, decreased to less than 20/120 within one half hour after instillation, and returned to 20/30 two hours later (Fig. 2, right).

Myopia—Average myopic changes for the group are shown in Figure 3. The average refractive error during the first week both for eyes on placebo medication and those wearing the Pilo-20 system was essentially constant throughout the day, at +0.30 diopters and +0.25 diopters, respectively. During subsequent weeks of wearing a Pilo-20 system, the eye had essentially no refractive error.

Normal eyes showed average increases in myopia from about +0.50 diopters before 1% pilocarpine eyedrops at 8 AM to −2.00 diopters at 8:30 AM and then decreasing to −0.60 diopters at 9 AM and to +0.25 diopters at 10 AM. In the afternoon and evening, the average refractive error in-

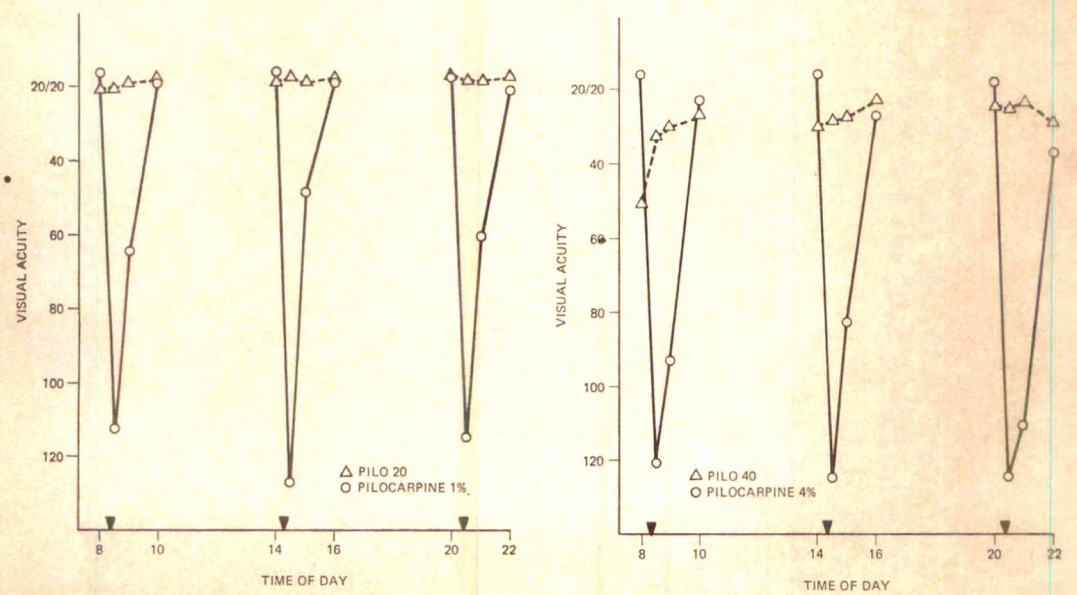
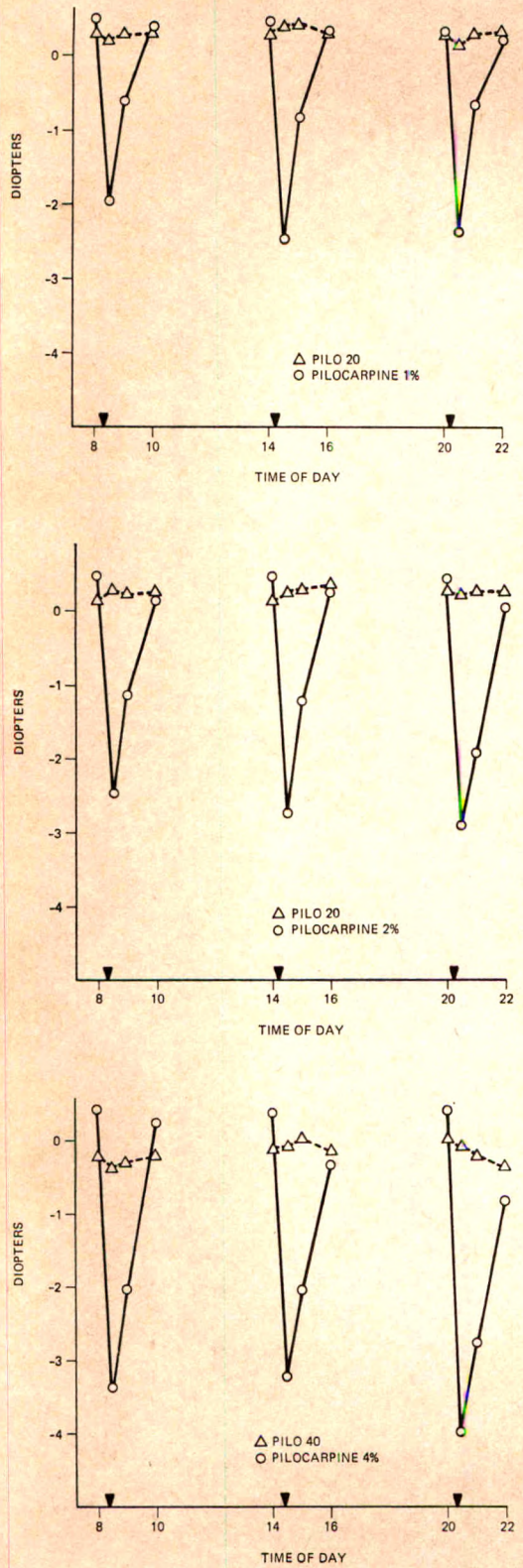


Fig. 2 (Place and associates). Left, Average visual acuity (Snellen chart) in six normal volunteers receiving 1% pilocarpine eyedrops given at the time indicated (arrow) and wearing a Pilo-20 system for seven days. Measurements made on days 2, 4, and 7. Right, Average visual acuity (Snellen chart) in six normal volunteers receiving 4% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-40 system for seven days. Measurements made on days 2, 4, and 7.



creased from +0.50 diopters (preinstillation) to about −2.50 diopters within one half hour after 1% pilocarpine eyedrop instillation, and decreased to zero diopters two hours afterward (Fig. 3, top). Eyes receiving 2% pilocarpine eyedrops had similar patterns of refractive changes which were of greater magnitude (Fig. 3, center).

Eyes wearing the Pilo-40 system had a fairly constant refractive error of about −0.20 diopters. With 4% pilocarpine eyedrops, eyes showed rapid increases in myopia from +0.30 diopters preinstillation to −3.20 to −4.00 diopters one half hour after therapy. Two hours after the morning eyedrops, the myopia had decreased to zero but two hours after the afternoon and evening eyedrops, myopia was −0.30 and −0.80 diopters (Fig. 3, bottom).

Miosis—The average degree of miosis produced by 1, 2, and 4% pilocarpine eyedrops and by Pilo-20 and Pilo-40 systems is summarized in Figure 4. The pupil-percent of iris diameter was essentially constant at 52% for both placebo unit and polyvinyl alcohol (Liquifilm Tears). The pupil-percent of iris diameter of the eyes wearing a Pilo-20 system remained fairly constant at about 40%. In contrast, pupils with the same proportional diameter before receiving 1% pilocarpine eyedrops showed a rapid decrease to around 20% one half hour after instillation; the pupil diameter gradually returned to 40% of iris diameter six hours after in-

Fig. 3 (Place and associates). Top, Average refraction for six normal volunteers receiving 1% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-20 system for seven days. Measurements made on days 2, 4, and 7. Center, Average refraction for six normal volunteers receiving 2% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-20 system for seven days. Measurements made on days 2, 4, and 7. Bottom, Average refraction for six normal volunteers receiving 4% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-40 system for seven days. Measurements made on days 2, 4, and 7.

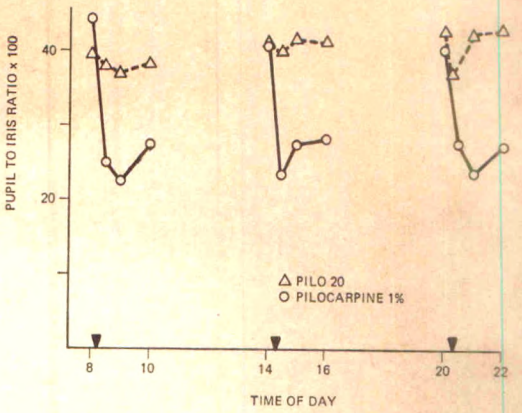
stillation (Fig. 4, top). The degree of miosis in normal volunteers produced by 2 and 4% pilocarpine eyedrops (Fig. 4, center) is similar to that caused by the 1% pilocarpine eyedrops.

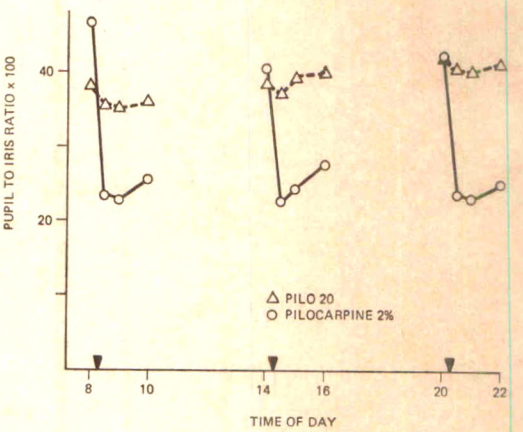
The Pilo-40 system produced a miosis that was practically constant, as the pupil-percent of iris diameter was 26% for the morning hours and 33% for the afternoon and evening hours (Fig. 4, bottom). The 4% pilocarpine eyedrops produced a rapid increase in miosis for one half hour after instillation; for the next 1½ hours, miosis remained about the same. A miotic effect was still present six hours after the eyedrops were given (Fig. 4, bottom).

Discussion

The six volunteers varied in their responsiveness to pilocarpine; one, a 35-year-old black man with brown eyes, was essentially unresponsive to it. Omission of data on this volunteer increases the differences between the results obtained with eyedrops and with the therapeutic systems. Volunteers with blue eyes appeared more responsive to pilocarpine than those with brown eyes, an observation reported previously.[8]

In these six normal subjects the 2 and 4% pilocarpine eyedrops or the Pilo-40 system did not produce a greater hypotensive effect than the 1% pilocarpine eyedrops or the Pilo-20 system. In patients with glaucoma the





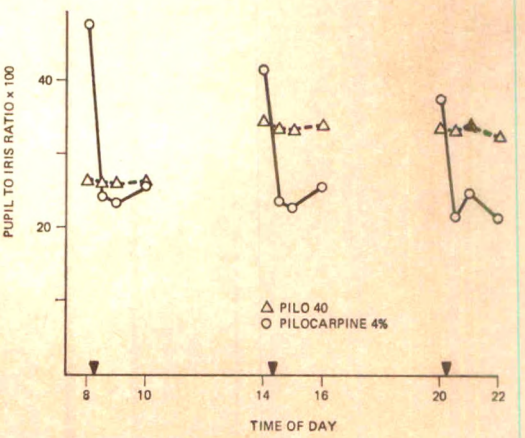


Fig. 4 (Place and associates). Top, Average pupil-percent of iris diameter for six normal volunteers receiving 1% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-20 system for seven days. Measurements made on days 2, 4, and 7. Center, Average pupil-percent of iris diameter for six normal volunteers receiving 2% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-20 system for seven days. Measurements made on days 2, 4, and 7. Bottom, Average pupil-percent of iris diameter for six normal volunteers receiving 4% pilocarpine eyedrops given at the times indicated (arrow) and wearing a Pilo-40 system for seven days. Measurements made on days 2, 4, and 7.

more concentrated eyedrops and the Pilo-40 system have a greater hypotensive effect than 1% pilocarpine eyedrops or the Pilo-20 system.

During the untreated and placebo periods normal intraocular pressures showed a diurnal decrease from 17.0 mm Hg at the morning sessions (8 to 10 AM), to 15.7 mm Hg at the afternoon sessions (2 to 4 PM), and to 14.0 mm Hg at the evening sessions (8 to 10 PM). This magnitude of diurnal variation also occurred, in addition to a lowering of intraocular pressure, when the subjects received pilocarpine, either as eyedrops or from an ocular therapeutic system. The difference in intraocular pressures between untreated and pilocarpine-treated eyes, however, appeared to be less in the afternoon and evening than in the morning (Table 3).

The differences between the effects on visual acuity of eyedrops and the ocular therapeutic system are essentially the same in the morning, afternoon, and evening. Myopic changes, however, appeared longer lasting with eyedrops later in the day than during the morning.

The more intense visual effects of eyedrops increased with increased concentrations (except for miosis). Because the changes also varied widely over time, they were impossible to rectify by a lens. The variability of these effects is shown by the large standard deviations. (Although reproducibility of each effect in the same volunteer at the same time on different days was good, large differences occurred from one volunteer to another). In contrast, the eyes adjusted to the smaller, more constant visual changes produced by both ocular therapeutic systems. Volunteers using the systems functioned without any visual handicaps and did not require corrective lenses.

Summary

Normal volunteers used 1, 2, and 4% pilocarpine eyedrops, three times daily, or ocular therapeutic systems placed in the conjunctival cul-de-sac to control intraocular pressure. The systems continuously released 20 and 40 μg/hour of pilocarpine for one week. Although the amount of drug delivered to the eye from the ocular therapeutic system was one fifth that obtained from the eyedrops, the decrease of intraocular pressure was comparable. The ocular therapeutic systems produced small, constant effects on visual acuity, refractive error, and miosis that did not cause visual handicaps or require correction. The effects of eyedrops on these visual factors were large and varied and produced marked visual handicaps that were not correctable with spectacles. Despite its comparable hypotensive effect in normal subjects, continuous delivery of pilocarpine by means of an ocular therapeutic system elicits less severe side effects than pilocarpine eyedrops.

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THE BLOOD-AQUEOUS BARRIER IN FIVE SPECIES

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Studies on the permeability characteristics of the tissues and vessels that surround the aqueous chambers of the eye contribute to the understanding of the blood-aqueous barrier and the composition of the aqueous humor.

Recent electron microscopy investigations of the tissues and vessels related to the aqueous chambers have revealed ultrastructural details of importance in the study of hematic barriers, such as a great variety of cellular junction complexes, including "tight" junctions that may prevent the passage of certain substances and which were found in the ciliary epithelium,[1-9] corneal endothelium,[10,11] (except in frogs[12] and some monkeys[13]), and endothelium of the iridoscleral angle.[14-18]

Conversely, ultrastructural findings include the presence of the intercellular clefts or cellular fenestrations, or both, in the capillary endothelium of the ciliary body,[1,8] endothelium of the iridoscleral angle,[14-18] and in the iridial endothelium[19-21] and the iridial epithelium[19,20] of some species. These openings may permit an easy diffusion of fluids, solutes, and suspensions.

Electron microscopy tracing of electron-opaque particles injected into the systemic blood, notably horseradish peroxidase, has pointed out that the anatomic sites of the barriers for these large molecules in the ciliary epithelium,[7-9,22] iridial vascular endothelium,[7-9,23] and corneal endothelium[10,11,24,25] are located mainly at the level of the intercellular tight junctions.

Barriers to free diffusion movements of solutes and solvents (fluid electrolyte pump systems) have also been detected in the ciliary epithelium[26-29] and cornea[13,30,31] by using in vitro investigations of these structures.

In this study, I investigated the in vivo permeability properties of the tissues and vessels bordering the aqueous chambers of the eye, using acriflavine neutral as a tracer, with a small molecular weight (224). It has been proven that the passage of this compound through hematic barriers, including the blood-aqueous barrier, is restricted.[32-37]

MATERIAL AND METHODS

Rhesus monkeys, cats, rabbits, turtles, and pigeons were used in the present study. Each species has ocular anatomic peculiarities. Rhesus monkeys and cats have a fully vascularized retina, rabbits have a partially vascularized retina and portions of their ciliary processes are implanted on the dorsal iridial surface, turtles and pigeons have an avascular retina, and pigeons possess a prominent and richly vascularized intravitreal organ, the pecten.

Each species was divided into three groups according to the type of acriflavine neutral injection received—intravenous or intraperitoneal, intra-aqueous, and intravitreal.

Acriflavine neutral is a mixture of 3, 6-diamino 10 methylacridinum chloride and 3, 6-diaminoacridine. I chose this substance from the diaminoacridine group because of its combined undetectable toxicity at the dose levels I employed, its bright and lasting fluorescence produced by itself or after combining with in vivo nuclear DNA and RNA,[38-40] and its inability to cross through hematic barriers.[32-37,41]

The standard doses chosen and administered through intravenous or intraperitoneal injections were 20 mg/kg of body weight in a 1.5% isotonic saline solution. These

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standard doses result in a 3.38×10^{-6}M blood concentration of free circulating acriflavine.[36] The intra-aqueous and intravitreal injections were a 3.38×10^{-5}M of acriflavine neutral in isotonic saline solution in a volume equal to one tenth of the total aqueous humor or vitreous volume. Thus, the final concentration of acriflavine in the ocular fluids was 3.38×10^{-6}M, the same as in the blood after the standard intravenous and intraperitoneal injections.

To avoid breaking the aqueous barrier with the intra-aqueous or intravitreal injections, three fourths of the total thickness of the cornea or sclera was incised 2 mm in length with a sharp corneal scalpel before the introduction of a 26-gauge needle into the aqueous or vitreous chambers. In all cases the injections were done simultaneously with a retrieval of aqueous humor in a volume equal to that of the injection of acriflavine solution.

All animals were anesthetized with pentobarbital sodium, the eyes were rapidly enucleated one hour after the acriflavine injections, and 1-mm^3 pieces of tissue containing part of the aqueous chamber walls and its neighboring tissues were instantaneously ultrafrozen at −180°C by dropping them into isopenthane immersed into liquid nitrogen.

The tissues were transferred into a custom-made freeze dryer where they were dried by sublimation at −50°C in a vacuum of 10^{-4} mm Hg and embedded in Paraplast while in the same vacuum.

The tissues were sectioned, 5 to 8 μ thick, mounted, examined under a fluorescence microscope, and photographed in black and white and color.

Additional subgroups of animals, composed of the same species used in the previous three main groups, received intravenous, intraperitoneal, intra-aqueous, or intravitreal injections of acriflavine neutral in the same or greater volumes, but always in greater concentrations. These injections were administered in a single dose or repeated doses on consecutive days.

The eyes of these additional animals were enucleated three minutes to three hours after the intravenous, intraperitoneal, or intraocular injections. All the tissues from these animals were prepared in the manner described.

A fluorescence microscope was used for this study. The illumination was provided by a high vapor pressure mercury lamp. The exciting light was attained by allowing the light of the mercury lamp to pass through a No. 5113 glass Corning filter with a light transmission peak at 410 mμ wavelength and a 30% light transmission at approximately 365 mμ wavelength, which is necessary to excite the free and bonded acriflavine. A secondary glass Corning No. 3486 filter was used to absorb all light below 500 mμ wavelength and to permit the light above 500 mμ wavelength to pass, including that of the fluorescent light produced by the acriflavine, either free or bonded, to nuclear DNA and RNA.

Both the aqueous humor and vitreous body were frozen in vivo and in situ, their surrounding tissues were carefully removed, and then both were melted and examined fluoroscopically. An ultraviolet light fluorometer and primary and secondary glass Corning filters were used to search for the presence or absence of acriflavine in the aqueous humor and vitreous body. With this fluorometer it was possible to detect dilutions of acriflavine neutral to 10^{-10}. In some animals the aqueous humor was not frozen in situ, but was obtained by paracentesis of the aqueous chambers and then examined in the fluorometer. The animals receiving intravitreal injection were examined one to nine hours after the injections.

Results

Intravenous and intraperitoneal injection group—Nuclear fluorescence was found in all tissues and vessels that surround the aqueous chambers; however, fluorescence was not detected in the aqueous humor.

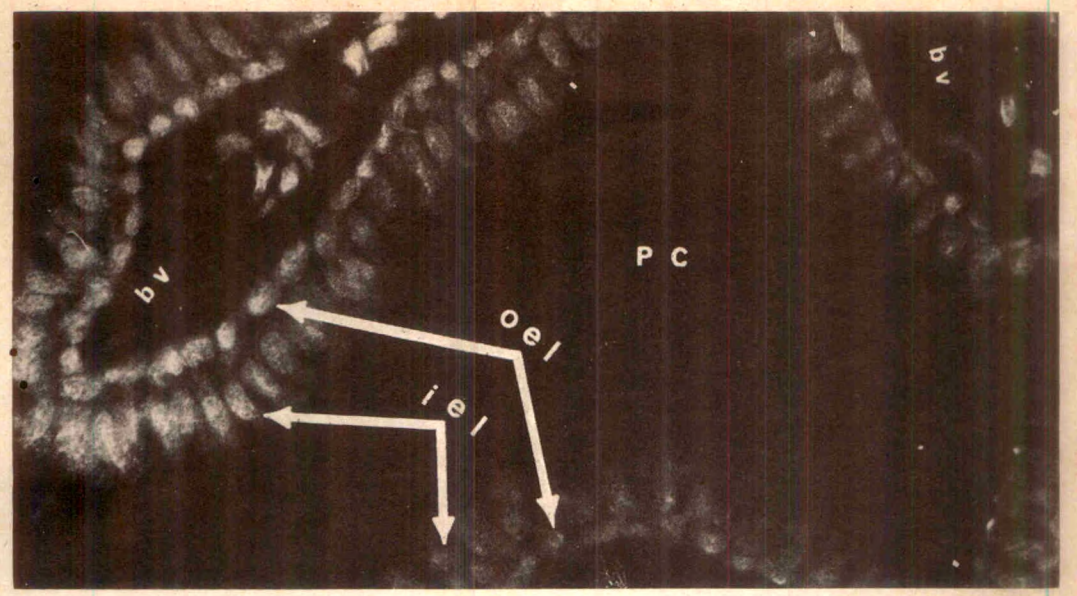


Fig. 1 (Rodriguez-Peralta). Rabbit ciliary epithelium. The cell nuclei of the outer epithelial layer (oel), inner epithelial layer (iel), blood vessels (bv), and stroma are fluorescent. Fluorescence was not detected in the aqueous humor of the posterior chamber (PC). An intravenous injection of acriflavine neutral produced a 3.38 × 10^{-6}M concentration in the circulating blood, one hour after the injection (freeze-dried, ×600).

Intense fluorescence was present in the nuclei of all walls of the blood vessels, stroma, and in the nuclei of the two layers of the ciliary epithelium (Fig. 1). Fluorescence was not detected in the ciliary epithelium of the pigeon (Figs. 2 and 3). The nuclei of all tissues and vessels of the iris and iridoscleral angle were fluorescent including those of the two layers of the iridial epithelium and those of the endothelium (Figs. 4-6). All nuclei of corneal endothelium, stroma, and epithelium were fluorescent (Fig. 7).

Fluorometric examination of the frozen aqueous humor and vitreous body failed to show any traces of acriflavine after they were melted.

The aqueous humor obtained by paracentesis of the aqueous chambers was consistently fluorescent, but the concentration of acriflavine was always far below 3.38 × 10^{-6}M, which is the concentration of free acriflavine in the circulating blood, and which corresponds to the nuclear fluorescence of the ocular tissues one hour after the intravenous or intraperitoneal injections of the dye.

The pattern of fluorescence in the nuclei of intraorbital, scleral, and choroidal tissues and vessels, and in the pigmented epithelium of the retina, and the absence of nuclear fluorescence in the tissues of the retinal pecten and in the vitreous body, have been reported previously.[35,36]

Intra-aqueous chamber injections—The effects of this type of injection on the surrounding tissues of the aqueous chambers resembled those seen after the intravenous or intraperitoneal injections. Intense nuclear fluorescence was found in the ciliary body tissues and vessels (Fig. 8), in the iridial and iridoscleral vessels and tissues including the endothelium (Figs. 9 and 10), and in the corneal tissue (Fig. 11).

In addition, fluorescence was present in the vitreous body with an intensity that decreased from the zonula area toward the posterior part of the vitreous body.

Intravitreal injections—The fluorescence

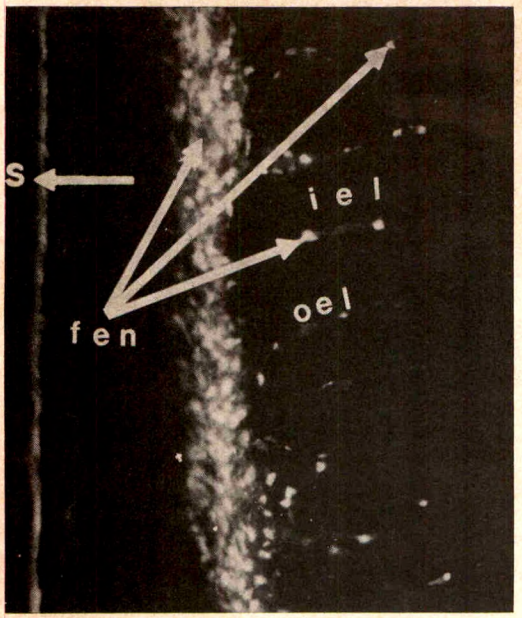


Fig. 2 (Rodriguez-Peralta). Pigeon ciliary epithelium. Fluorescence is noticeable in the thick sclera (S), but there is an intense nuclear fluorescence in the intravascular erythrocytes (fen). However, nuclear fluorescence is not present in the outer epithelial layer (oel) or inner epithelial layer (iel). Fluorescence was not found in the aqueous humor. An intravenous injection of acriflavine neutral produced a 3.38×10^{-6}M concentration in the circulating blood, one hour after injection (freeze-dried, ×240).

in the vitreous bodies one hour after the injection had a wide conical pattern; it looked as if a small wide-angle flashlight located at the site of the injected acriflavine was directing its light beam toward the fundus of the eye. Thus, the acriflavine solution moved toward the retina and optic nerve head, but not toward the posterior chamber. Flourescence was not found in the aqueous humor.

Similar results were found in the living animals I examined two to nine hours after the posterior eye chamber injections. The conical fluorescence pattern in these animals decreased in size and intensity until the ninth hour, when it disappeared.

A complete account of the results produced by this type of injection on tissues and vessels that surround the vitreous chamber in each of these five species has been reported previously.[36]

Injections of greater doses and concentrations of acriflavine neutral—Intravenous, intraperitoneal, intra-aqueous, or intravitreal injections of greater concentrations and volumes of acriflavine solutions, and the examination of the ocular tissues after the acriflavine injections, produced practically the same results in regard to the aqueous barriers as those observed in the animal groups that received standard doses and had their ocular tissues removed one hour after the acriflavine injections. The difference was that the intensity of the fluorescence increased with the higher doses and decreased as the time elapsed after the dye injections.

The intensity of the fluoresence in the cell nuclei of living animals usually decreased

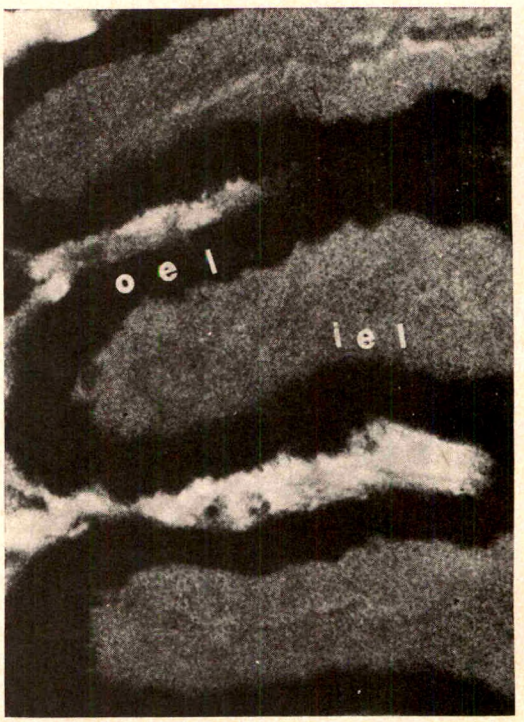


Fig. 3 (Rodriguez-Peralta). Higher magnification of ciliary processes of pigeon fails to show any nuclear epithelial fluorescence in the outer (oel) or inner (iel) layers. An intravenous injection of acriflavine neutral produced a 3.38×10^{-6}M concentration in the circulating blood, one hour after injection (freeze-dried, ×580).

rapidly 70 minutes after the injection of the dye.

The pattern produced by the distribution of the acriflavine injected into the aqueous humor or vitreous body of dead animals, or of animals that died immediately after the injection, was different from that of the living animals. The acriflavine slowly spread from the site of injection in all directions and was never eliminated from the vitreous and aqueous chambers.

Discussion

Eyes from the five species used in the present study were chosen because of certain differences in their anatomic and physiologic characteristics, such as those in the choroidal and retinal blood supply and in the localization of the hematic and fluid barriers in the vitreous chambers[36]; in special organs (the pecten in the pigeons); the location of the ciliary epithelium[42]; and the structure of the tissues of the iris[19,42] and iridoscleral angle.[18] Accordingly, I wanted to ascertain whether or not individual differences also exist as to the sites and characteristics of the blood-aqueous barriers of these various species, as well as differences in the passage of substances from the aqueous humor into

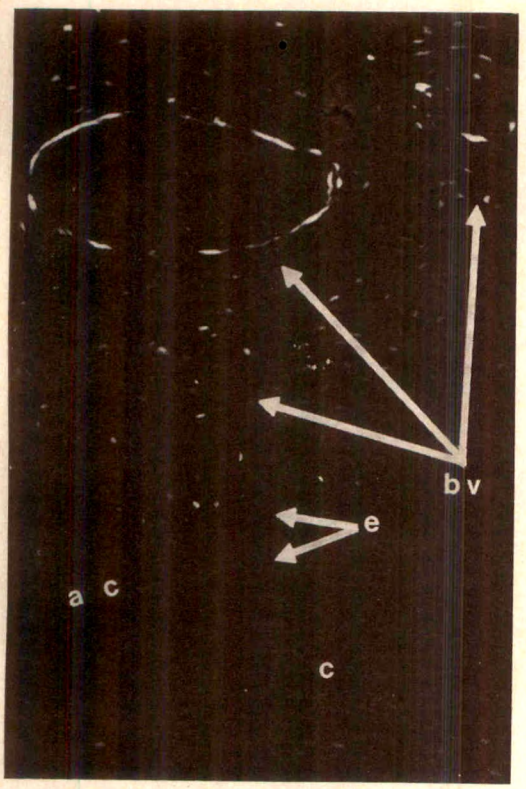


Fig. 4 (Rodriguez-Peralta). Iris and anterior chamber (ac) of rabbit. Nuclear fluorescence is present in the blood vessel walls (bv), stroma, and endothelium (e) of the anterior chamber; fluorescence was not detected in the aqueous humor. Cornea (c). An intravenous injection of acriflavine neutral produced a 3.38 × 10^{-6}M concentration in the circulating blood, one hour after injection (freeze-dried, ×220).

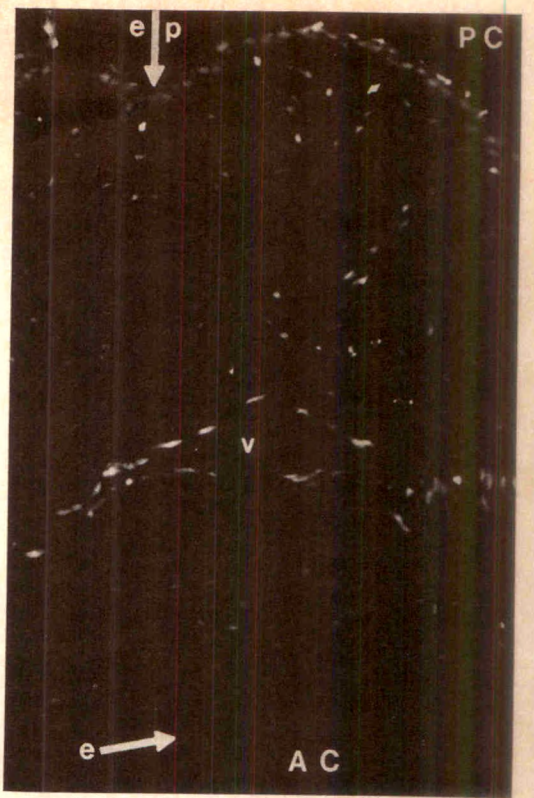


Fig. 5 (Rodriguez-Peralta). Rabbit iris. Blood vessels (v), endothelial (e), epithelial (ep), and connective tissue nuclei are fluorescent, but fluorescence was not found in the aqueous humor of posterior (PC) or anterior (AC) chambers, when aqueous was frozen in situ, isolated from its surrounding tissues, thawed, and then examined fluorometrically. Intravenous injections of acriflavine neutral produced a 3.38 × 10^{-6}M concentration in the circulating blood, one hour after injection (freeze-dried, ×250).



Fig. 6 (Rodriguez-Peralta). Iridoscleral angle of a rabbit. Nuclei of trabecular meshwork (tmw), surrounding the spaces of Fontana, and ciliary body stroma are intensely fluorescent. An intravenous injection of acriflavine neutral produced a 3.38 × 10^{-6}M concentration in the circulating blood, one hour after injection. AC indicates anterior chamber (freeze-dried, ×180).

the surrounding tissues, vessels, or vitreous body.

Acriflavine neutral (like other diaminoacridines) has been proved nontoxic at the dose level used in the studies of the hematic barriers, and it possesses specific affinity for all living nuclear DNA and RNA to which it becomes strongly bonded.[34-36,38-40]

Intravenous or intraperitoneal injections of acriflavine neutral at the dose level of 20 mg/kg of body weight (the standard dose level in this study) produce a 3.38 × 10^{-6}M concentration of free dye in the circulating blood.[36] The acriflavine passes instantaneously through the blood vessel walls into all tissues and fluids of the body that are not surrounded by hematic barriers.[36]

I chose the standard acriflavine dose level and the standard removal of the ocular tissues one hour after the injections to establish valid comparisons of the intensity of the fluorescence in the tissue nuclei and in ocular fluids.

The results in the animal subgroup that received greater doses and concentrations of the dye and whose ocular tissues were removed at various intervals after the acriflavine injections demonstrate that the tissue fluorescence intensity increases with the doses and decreases according to the length of time after the injections, although the barriers remain intact.

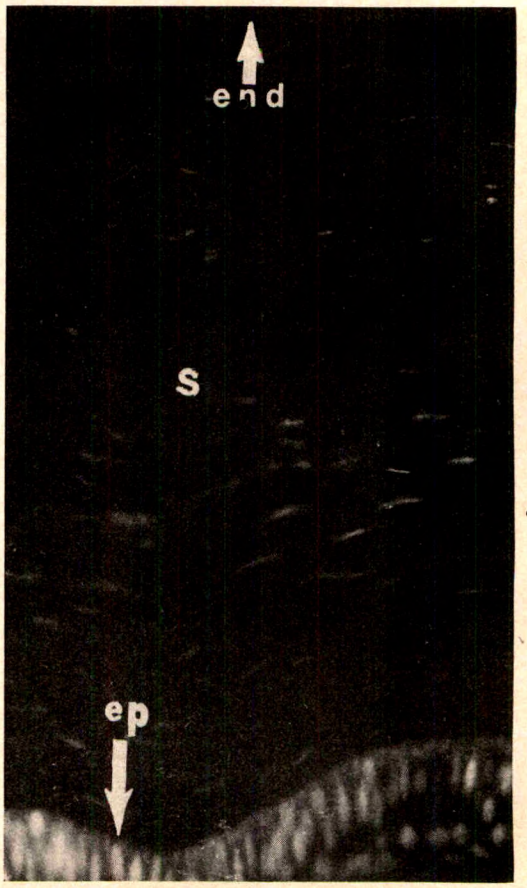


Fig. 7 (Rodriguez-Peralta). Monkey cornea. Endothelial (end), stroma (S), and epithelial (ep) nuclei are fluorescent. No fluorescence was found in the aqueous of the anterior chamber. An intraperitoneal injection of acriflavine neutral produced a 3.38 × 10^{-6}M concentration in the circulating blood, one hour after injection (freeze-dried, ×200).

Acriflavine neutral, either free or bonded to DNA and RNA, is excited by light of wavelengths close to 365 mμ, and it produces an intense fluorescence of wavelengths close to 530 mμ.

The molecular size of the acriflavine is too small (224 mol. wt.) to be electron-opaque, directly visualized, and traced. However, its fluorescence properties permit tracing and ascertaining the in vivo passage of its small molecules through the body tissues and fluids, and through the cell plasma membrane and the nuclear membrane in order to enter into the cell nuclei and to combine specifically with nuclear DNA and RNA.

Thus, by tracing the acriflavine fluorescence in its penetration through the tissues and into the cell nuclei of living organisms

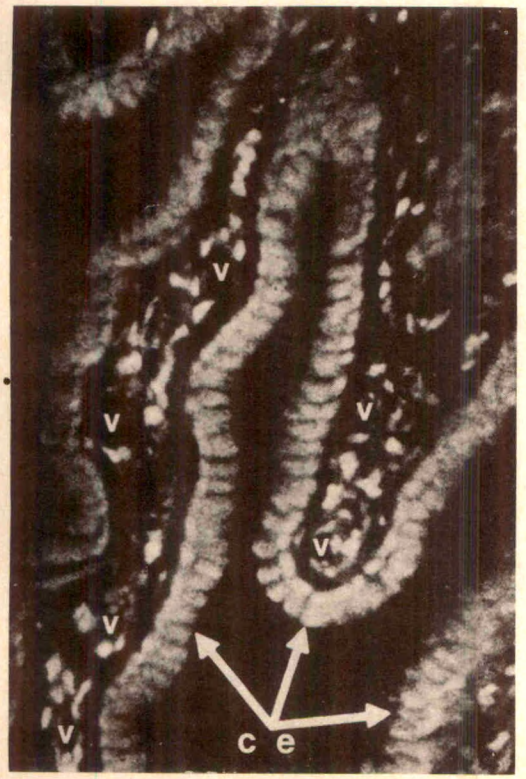


Fig. 8 (Rodriguez-Peralta). Ciliary processes of a rabbit. Bright nuclear fluorescence is present in both ciliary epithelial layers (ce) and in the stroma and blood vessels (v). A posterior chamber injection of acriflavine neutral produced a 3.38×10^{-6}M concentration in the aqueous humor, one hour after injection (freeze-dried, ×360).



Fig. 9 (Rodriguez-Peralta). Cat iris. Intense nuclear fluorescence in iridial endothelium (e), iridial stroma, and blood vessel walls (v). An intra-aqueous injection of acriflavine neutral produced a 3.38×10^{-6}M concentration in the aqueous humor, one hour after injection (freeze-dried, ×360).

to the sites where this fluorescence is stopped, the precise location of hematic barriers will be determined.

The in vivo tracing was successfully accomplished by suspended animation produced by instantaneously ultrafreezing small bits of tissues taken rapidly from the living animals under anesthesia one hour after intravenous or intraperitoneal injections. The subsequent preparation of these tissues avoids the displacement of the tracer from its original in vivo location and prevents tissue molecular turmoil that occurs after the use of chemical solutions that are generally employed in the preparation of tissues for light or electron microscopy.

The results of the intravenous or intraperitoneal injections of acriflavine neutral administered to the five species show that an intense nuclear fluorescence of all the

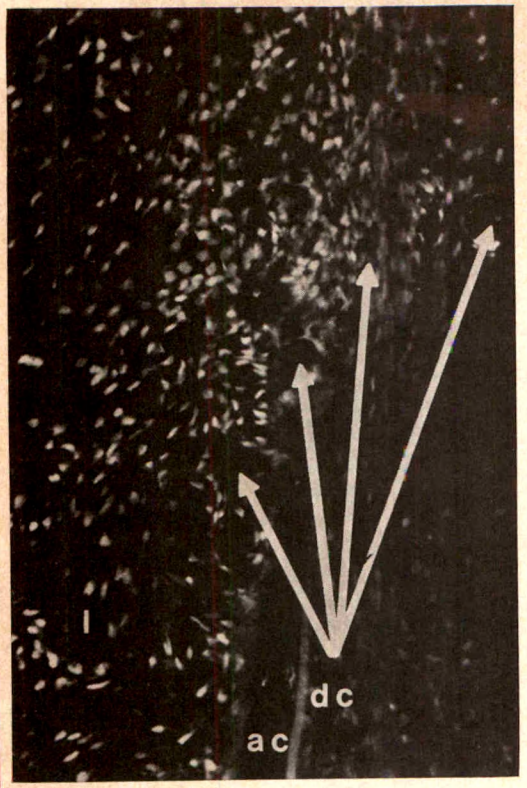


Fig. 10 (Rodriguez-Peralta). Iridoscleral angle of a rabbit. Nuclear fluorescence is present in the iris (I), pectin area, and in the walls of the drainage channels (dc). Anterior chamber (ac). An intra-aqueous injection of acriflavine neutral produced a 3.38×10^{-6}M concentration in the aqueous humor, one hour after injection (freeze-dried, ×180).

tissues surrounding the aqueous chambers was present, and that no fluorescence was detected in the aqueous humor. Such results indicate that barriers for the acriflavine neutral, present in these tissues, prevent its penetration into the aqueous fluid.

Thus, I systematically examined each of the structures circumscribing the aqueous chambers to retrace in logical sequence the pathways followed in the rapid tissue penetration of the dye to the sites of the barriers.

Ciliary body—In the ciliary body of monkeys, cats, rabbits, and turtles, the acriflavine neutral readily passed through the walls of the ciliary blood vessels and entered the stroma, combining with nuclear DNA and RNA (Figs. 1 and 6). Then it crossed through the basal and apical cell membranes of the pigmented epithelium, the apical cell membrane of the inner ciliary epithelium, and entered the nonpigmented epithelial cells. This path is ascertained by the bright nuclear fluorescence of both epithelial layers (Figs. 1 and 6); however, the dye failed to pass through the basal cell membrane of the nonpigmented epithelium into its basement lamina and into the aqueous humor, despite the increased intracellular content of acriflavine as indicated by the intense nuclear fluorescence (Fig. 1).

The absence of fluorescence in the aqueous humor also means that the dye does not seep along the intercellular spaces of the inner ciliary epithelium. These intercellular spaces are formed by the interdigitating lateral membranes of adjacent inner epithelial cells.[1,4–6,22] Two types of barriers have been described in relation to these spaces: structural and physiologic.

The continuous circular belts of zonula occludens junctions located near the apical surface of the cells[6,7,9,22] are responsible for the structural barrier; the fluid electrolyte pump systems, with activating ATPase located on the adjacent lateral cell membranes and possibly also in the intercellular space itself,[43,44] are responsible for the physiologic barrier.

The morphologic barrier forms an absolute barrier for the passage of large horseradish peroxidase molecules[7–9,22] and possibly for other molecules as well, while the physiologic barrier deals with the active selection and transport of substances to form the aqueous humor.[27,29] This barrier can be inactivated by ouabain.[45]

Whether either one or both barriers prevent the passage of acriflavine is not known. The dye does not seem to enter the intercellular spaces from the nonpigmented epithelial cells across the lateral membranes or from the ciliary intercellular apical space (that the dye crosses to enter the inner epithelial layer), for otherwise the dye would

pass into the aqueous humor and fluorescence would be present.

Thus, the sites of the blood-aqueous barrier for the acriflavine neutral in the ciliary body are located at the levels of the basal cell membrane of the nonpigmented epithelium and in the lateral intercellular spaces.

In the pigeon, fluorescence was not found in any of the ciliary epithelium nuclei (Figs. 2 and 3). In this species, the hematic barrier is located in the basal membrane of the outer layer of the ciliary epithelium (Figs. 2 and 3) and in the intercellular junctions. No ultrastructural or fine physiologic studies of the ciliary epithelium in the pigeon have been reported.

Iris and anterior chamber angle—Acriflavine neutral rapidly passed through the blood vessel walls and stroma of these structures as demonstrated by their bright nuclear fluorescence (Figs. 4-6). It continued into the two layers of the iridial epithelium (Figs. 4 and 5) and the endothelium lining the anterior surface of the iris (Fig. 5) and of the angle (Fig. 6); but fluorescence was not detected in the aqueous humor. Thus, a barrier that prevents the passage of acriflavine neutral into the aqueous fluid is present and is located at the level of that part of the epithelial and endothelial cell membranes that faces the aqueous chambers.

The iridial vascular endothelium presents no barrier for the acriflavine despite the presence of tight intercellular junctions which some investigators have found to be a barrier for the passage of large horseradish peroxidase molecules.[7,9,23]

Conversely, the results of ultrastructural studies show the iridial epithelium and endothelium of the iridial and iridoscleral angle of some species (man, rhesus monkeys, and rats) are formed by discontinuous cellular membranes with pores, holes, and crypts between adjacent cells that extend to the stroma in the iris.[19-21]

Nevertheless, the results of this study show that acriflavine neutral does not pass through that part of the cell membrane facing the chambers or through the intercellular junctions. Consequently, further investigations of the structural and physiologic characteristics of these cell junctions in several species may completely explain why the acriflavine does not pass through these intercellular spaces. These studies would show whether factors other than, or in addition to, the difference in hydrostatic pressures between aqueous humor and its draining episcleral and iridial veins[9,46] are present or not.

Cornea—All nuclei of corneal endothelium, stroma, and epithelium were fluorescent (Fig. 7). This fluorescence may be produced not only by the dye from the vascular limbal plexus, but from the acriflavine in the tears bathing the conjunctival sac. Nevertheless, the dye did not pass into the aqueous humor. The small acriflavine neutral molecule passed through the basal membrane of the corneal endothelium, into the cells, and into the nuclei (as indicated by their fluorescence), but it did not pass through the apical endothelial membrane. Thus, the site of the corneal barrier for acriflavine is located at the level of the apical endothelial membrane and also at the level of the intercellular junctions.

Some investigators reported the presence of circular tight junctions in the human and rabbit corneal endothelia[10,11] that prevented the passage of thorium dioxide injected into the aqueous chambers, although particles of this compound were believed to be transported inside vesicles around the tight junctions.[11] Recently, investigators using horseradish peroxidase and lanthanum nitrate injected into the anterior chamber reported the absence of tight corneal endothelial junctions and an easy intercellular passage of the tracers in the monkey and rabbit.[13] There have been no studies that showed the passage of these or similar compounds in the opposite direction.

Physiologic barriers consisting of fluid electrolyte pump systems have been detected

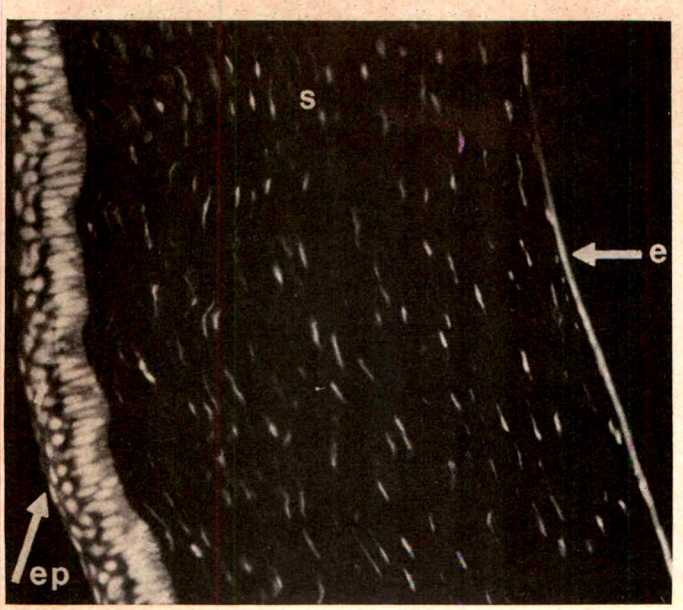


Fig. 11 (Rodriguez-Peralta). Monkey cornea. Nuclear fluorescence is present in the corneal endothelium (e), stroma (s), and epithelium (ep). An intra-aqueous injection of acriflavine neutral produced a 3.38×10^{-6}M concentration in the aqueous humor, one hour after injection (freeze-dried, ×120).

in the corneal endothelium of the rabbit[13,30,31] and monkey,[13] and ATPase reactions have been found in the lateral margins of the corneal endothelial cells and in their intercellular spaces.[47,48] I do not know whether these barriers are the ones responsible for preventing the passage of acriflavine through the corneal endothelium into the aqueous humor.

There are many unsolved problems concerning the restriction of the passage of substances, not only through the corneal endothelium but through any living hematic or tissue barrier. They involve complex mechanisms that are not completely understood and are not the same for all substances. Therefore, we must continue to follow a multiple approach that includes various methods and the use of several tracers.

Vitreous body—This study confirmed the results of previous studies.[36] Acriflavine neutral did not penetrate into the vitreous body when administered intravenously or intraperitoneally. To produce the same aqueous concentrations as those obtained in the blood after intravenous or intramuscular injection, injections of acriflavine administered in the posterior eye chamber resulted in an intense nuclear fluorescence of all tissues and vessels surrounding the aqueous chamber (Figs. 8-11).

These results are not due to the breakdown of the blood-aqueous barrier as in cases of paracentesis of the anterior chamber. The breakdown of the blood-aqueous barrier after the paracentesis of the anterior chamber of the eye, with or without simultaneous changes in the ultrastructure of the ciliary epithelium,[6,9] is the consequence of the sudden changes of pressure that follow one or repeated aspirations of most of the aqueous humor.[6,9]

The injection of a small amount of an isotonic acriflavine solution into the aqueous chamber with a simultaneous retrieval of the same amount of aqueous humor is not likely to produce the molecular and hydrostatic pressure changes that occur after paracentesis. The small amounts of aqueous humor extracted by paracentesis from the anterior chamber after the standard intravenous or intraperitoneal injections of acriflavine was consistently fluorescent, but the concentration of the dye in the aqueous chamber was below 3.38×10^{-6}M.

This decreased concentration in the aqueous chamber indicates that the restriction imposed by the barrier on the passage of

acriflavine from the blood into the aqueous humor had decreased but was not abolished. If the aqueous barrier exerted a similar degree of restriction on the passage of dye from the aqueous humor into the blood, and if the corneal puncture produced a partial breakdown of the aqueous barrier, then the nuclear fluorescence of the ocular tissues after intra-aqueous injections should be low; however, this is not the case, as demonstrated by the bright nuclear fluorescence (Figs. 8-11) which equals that obtained after standard intravenous or intraperitoneal injections.

Thus, the blood-aqueous barrier, like the hematoencephelic[32,33] and the hematic barriers of the optic nerve[34] and retina,[36] is impermeable (in one direction only) to the passage of the acriflavine from the blood into the aqueous humor, but is completely permeable in the reverse direction. In cats, monkeys, and rabbits, the acriflavine also passed readily from the posterior chamber into the vitreous body and moved mainly toward the optic nerve head to be eliminated through the blood vessels of this region. In turtles and pigeons, as their retinas are avascular, the elimination passed through retinal tissues into the choroidal vessels, and through the pecten vessels in the pigeon.[36] The ciliary and iridial epithelia constitute a common hematic barrier for the aqueous humor and vitreous body, forming a part of the blood-vitreous barrier.

The clear current of aqueous humor from the posterior chamber into the vitreous body toward the optic nerve head vessels constitutes an additional pathway of aqueous humor drainage. Interruption of this pathway may produce glaucoma, as in the case of damage and obstruction of the zonular trabecular meshwork resulting from injections of alpha-chymotrypsin in the posterior chamber of rabbits[49] and monkeys.[50]

In a similar way organic or physiologic changes of the optic nerve head vasculature could produce a retention or a reversal in the direction of the current of the vitreous fluids, also resulting in increased intraocular pressure.

The acriflavine injected into the vitreous body followed the same pattern of vitreous distribution and in vivo elimination as that coming from the posterior aqueous chamber, but the acriflavine never passed from the vitreous body to the aqueous humor. This indicates that under normal conditions the blood-vitreous barrier does not form a part of the blood-aqueous barrier.

The blood-aqueous barrier prevents the passage of acriflavine from the blood stream into the aqueous humor, but it permits a free passage in the opposite direction, that is, from the aqueous humor into the surrounding tissues and into the blood stream.

The blood-aqueous barriers in rabbits, turtles, monkeys, and cats have similar anatomic locations and characteristics; there is a different anatomic location of the barrier in the ciliary body of the pigeon.

The clear current of aqueous humor from the posterior chamber, passing through the zonula into the vitreous body toward the retina and optic nerve vessels, constitutes an additional pathway of aqueous humor drainage. Interruption of this pathway produced by anatomic or physiologic changes in the vitreous chamber or optic nerve head vasculature can result in glaucoma, as in the cases of damage to the zonula[49,50] or in other possible cases of open-angle glaucoma with or without optic nerve degeneration.

Summary

The in vivo sites of the blood-aqueous barrier were determined in five animal species, using acriflavine neutral (224 mol. wt.), ultrafreezing and drying, fluorescence microscopy, and fluorometry. Not toxic, acriflavine had specific in vivo affinity for nuclear DNA and RNA, produced intense fluorescence, and did not pass through hematic barriers. Acriflavine was given in doses to produce the same concentrations in the systemic blood or in the aqueous humor. The exact sites of the blood-aqueous barrier,

demonstrated by tracing the acriflavine fluorescence through tissues and individual cells, were in the basal cell membranes of inner ciliary and iridial epithelia and apical cell membranes of iridial and corneal endothelia.

Acriflavine passed freely from the aqueous humor into the blood stream. It also followed an aqueous flow into the vitreous body and optic nerve head vessels. Interruption or reversal of this flow may cause open-angle glaucoma.

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LENS CHANGES IN A GALACTOSEMIC FETUS

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The galactosemias are diseases caused by recessively inherited inborn errors of galactose metabolism. The severe systemic type of galactosemia was described first and is sometimes referred to as the "classic form." In this form, deficiency of the enzyme galactose 1-phosphate uridyl transferase results in an inability to metabolize galactose normally and leads to an accumulation of the galactose metabolites, galactose-1-phosphate and dulcitol.[1] Clinical manifestations of this deficiency appear soon after birth and include cataract formation, liver enlargement, jaundice, mental retardation, and failure to thrive. The zonular or nuclear lens changes that develop are always bilateral, and eventually the increased refractile power of the lens cells around the fetal nucleus gives the appearance of an oil droplet. The affected infant may die within a few days if galactose is not excluded from the diet.

Another type of galactosemia is caused by galactokinase deficiency. In this form the onset is insidious, and cataract is usually the sole clinical manifestation, although galactosuria occurs.

In the form of this disease characterized by a transferase deficiency, cataracts develop in about 75% of patients[2,3] and have been observed as early as the first few days after birth.[3] To our knowledge they never have been described in newborn infants, and it is generally believed that lens damage in galactosemia occurs after birth.

By means of the modern techniques of transabdominal amniocentesis and tissue culture, we can now make a prenatal diagnosis of galactosemia.[4] We report the ocular findings in a 5-month-old fetus obtained for study after a prenatal diagnosis of galactosemia had been made and a prostaglandin abortion induced.

CASE REPORT

The parents of the fetus were unrelated Spanish Americans. Their first child died, presumably of galactosemia, although unequivocal information on this point was not available to us. There had also been one healthy child and one miscarriage. At the third month of the pregnancy in question (the fourth), the parents asked their physician if the fetus might have galactosemia.

The first step was to determine the parents' red blood cell levels of galactose 1-phosphate uridyl transferase. The results showed that both mother and father had only one half the normal amount of the enzyme (Table). This suggested that both were heterozygous (carriers) for galactose 1-phosphate uridyl transferase deficiency and that the fetus had a 25% chance of being affected. In the 15th week of gestation a transabdominal amniocentesis was performed and the amniotic cells were cultured. When biochemical assays showed no galactose 1-phosphate uridyl transferase activity, a prenatal diagnosis of galactosemia was made.

A prostaglandin abortion was induced when the fetus was 5 months old. The diagnosis was confirmed by examination of the liver and lung tissues in which there was no detactable transferase activity. Galactose was found in these tissues, an abnormal finding indicating an inability to metabolize this sugar.

METHODS

The eyes were removed soon after the abortion, and one eye was placed in formalin and processed for light microscopy. The other was bisected into anterior and posterior segments. We removed the lens and a portion of the vitreous body and fixed them for two to three hours at room temperature in

From the Department of Ophthalmology (Drs. Vannas, Hogan, and Ms. Wood), Francis I. Proctor Foundation for Research in Ophthalmology, and the Department of Obstetrics and Gynecology (Dr. Golbus), University of California, San Francisco. Dr. Vannas was a Hearst Fellow, 1973-1974, Department of Ophthalmology. This study was supported in part by Public Health Service research grant EY 00799; National Institutes of Health grant GM-19527; National Foundation, March of Dimes grant CRBS-321; and Research to Prevent Blindness, Inc., New York.

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TABLE

RED BLOOD CELL TRANSFERASE LEVELS IN THE PARENTS OF A GALACTOSEMIC FETUS

Enzyme	Normal Levels (μM/g of Hgb/hr)	Mother	Father
Galactose 1-phosphate uridyl transferase	23.5 ± 2.5	10.2 10.4	11.0 11.1

3% glutaraldehyde-paraformaldehyde in 0.2M sodium cacodylate buffer, with the addition of 1% sucrose, 0.2% calcium chloride, and 0.5% potassium chloride, pH 7.4. Fixation was followed by postfixation for two hours in 2% osmium tetroxide in 0.28M sodium veronal acetate buffer, with the addition of sucrose. The tissue was then stained en bloc in 2% uranyl acetate with sodium hydrogen maleate buffer for two hours (to achieve contrast), dehydrated in acetone, and embedded in Araldite.

For orientation purposes, we cut 1 μ sections and stained them with uranyl acetate in

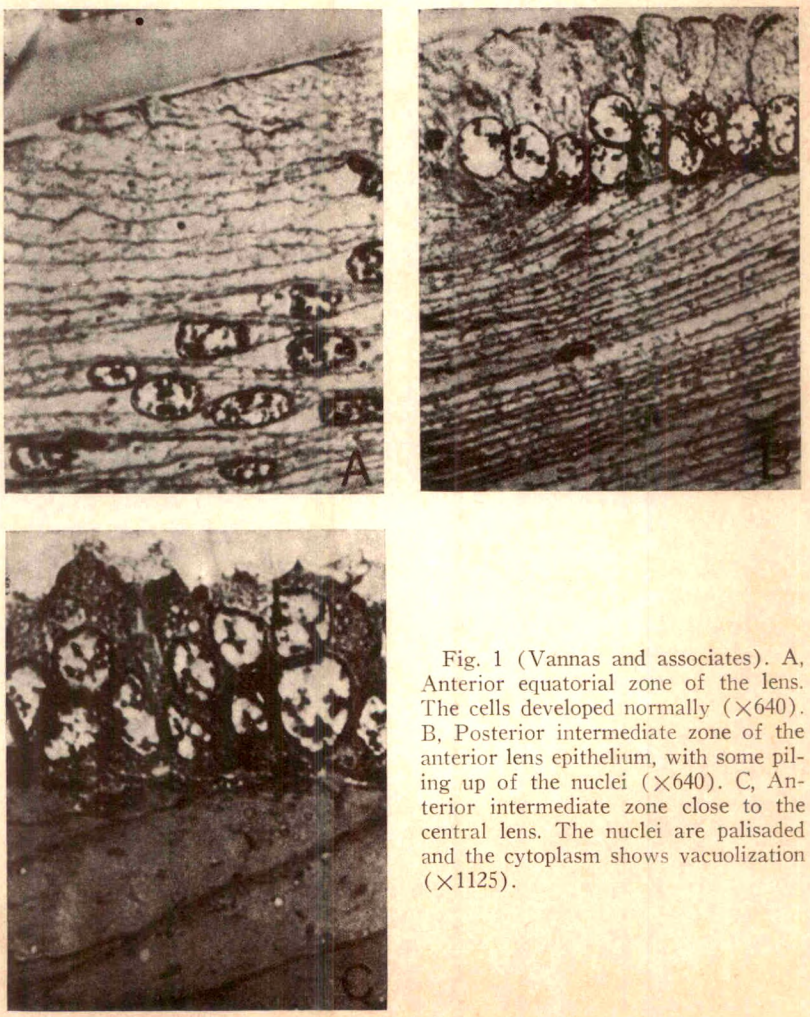
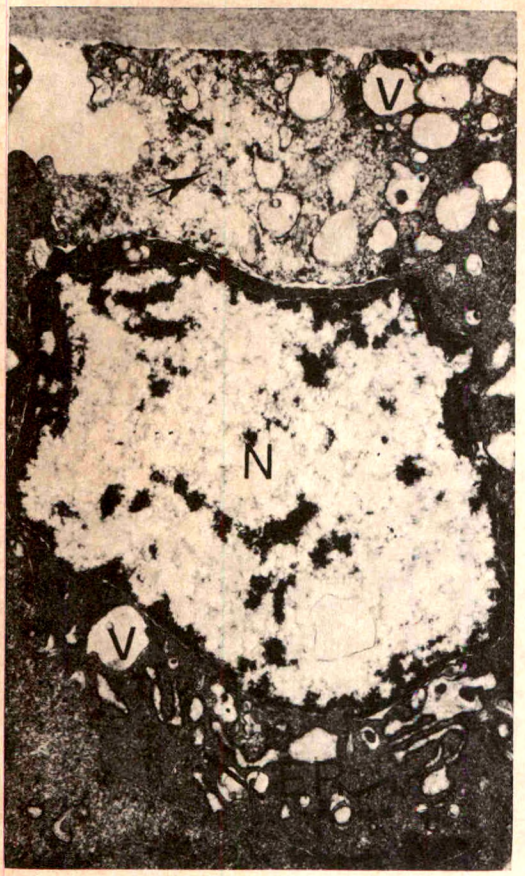


Fig. 1 (Vannas and associates). A, Anterior equatorial zone of the lens. The cells developed normally (×640). B, Posterior intermediate zone of the anterior lens epithelium, with some piling up of the nuclei (×640). C, Anterior intermediate zone close to the central lens. The nuclei are palisaded and the cytoplasm shows vacuolization (×1125).



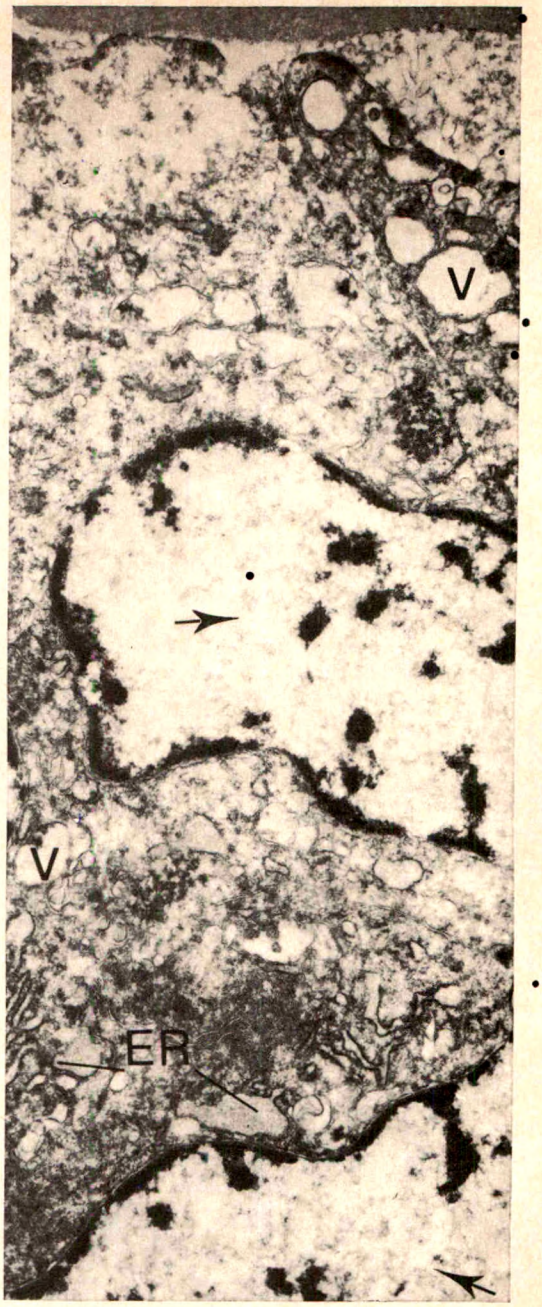


Fig. 2 (Vannas and associates). Above, Degenerating epithelial cells beneath the anterior capsule. Ribosomes are concentrated in this portion of the cell (arrow). Note the dense cytoplasm, numerous vacuoles (V), and dilated endoplasmic reticulum (ER); N indicates nucleus (×6,500). Right, Piling up of cells. The anterior cytoplasm and nuclei appear watery (arrows). There are many cytoplasmic vacuoles (V) and the endoplasmic reticulum (ER) is dilated (×13,600).

water and lead citrate and examined them with the Siemens-Elmiskop 1A microscope.

We prepared normal control lenses for electron microscopy from similarly induced prostaglandin-aborted fetuses of the same age by using the same method.

Results

On gross examination the eyes appeared normal and showed no developmental defects. Each measured 12 × 13 × 13 mm and the corneas were 6 × 5.5 mm in diameter.

By light microscopy the only pathologic

changes were in the lenses. The anterior and intermediate epithelial cells were crowded in some areas, often arranged in two to three layers (Fig. 1). The cytoplasm of some cells showed gross vacuolization (Fig. 1, C). Those closer to the equator appeared normal (Fig. 1, A). The cells in the posterior subcapsular zone stained more lightly and in an uneven fashion, as if somewhat hydropic.

By electron microscopy, the lens capsule was normal, but the lens epithelium in most areas showed marked degenerative changes. The density of the cells varied greatly: the cytoplasm of dying or dead cells was dark and osmiophilic, and in others it was watery and loosely granular (Fig. 2). In the latter cells the mitochondria were swollen and vacuolated and the sacs of the endoplasmic reticulum were dilated and filled with fine granular material. The nuclei were pale, and showed an uneven distribution of the nuclear chromatin.

The changes were less marked in the subepithelial lens cells. Their plasma membranes looked normal and had the usual intercellular junctions, and there was not much intercellular edema. The cytoplasm contained many vacuoles and the number of ribosomes apparently was increased (Fig. 3). The changes were less marked but similar in the equatorial area, and the degree of cell change varied from section to section (Fig. 4).

The posterior lens cells had lost some of their hexagonal appearance and looked rounded or irregular. Their density varied considerably compared to the normal lens cells: the liquefied cells were osmiophilic and homogenous, while adjacent cells showed a loosely granular cytoplasm (Fig. 5). Most of the cell membranes were preserved and showed tight junctions but there were occasional areas of intercellular edema.

The control lenses did not show any of these pathologic changes. The anterior lens

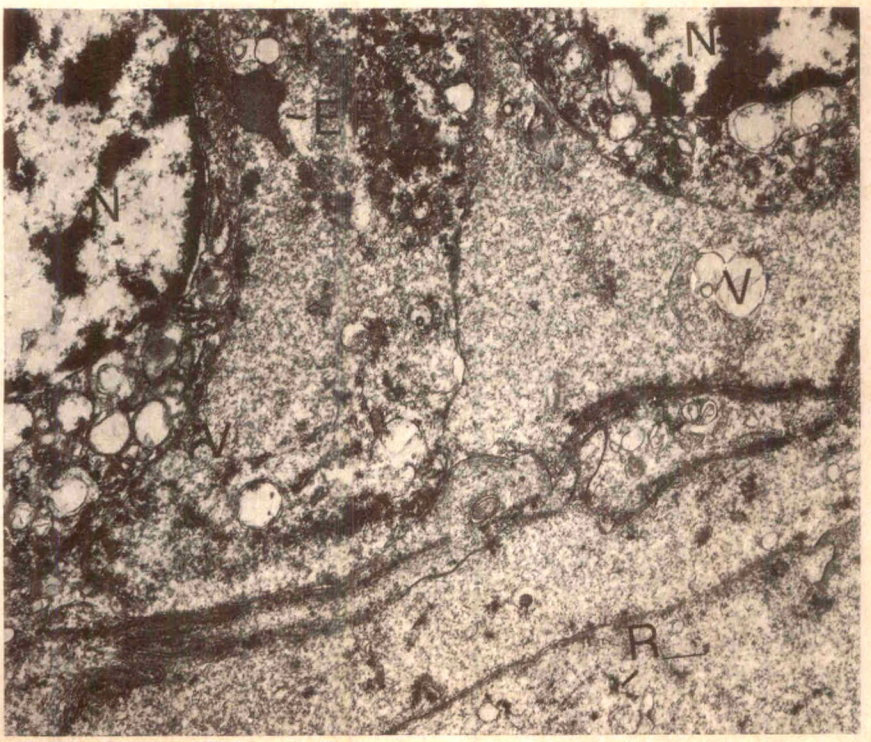


Fig. 3 (Vannas and associates). The anterior lens epithelium has small, clear, fluid-filled vacuoles (V) and a somewhat granular cytoplasm. There is widening of the sacs of endoplastic reticulum (ER); R indicates ribosomes; N, nucleus (×5,600).

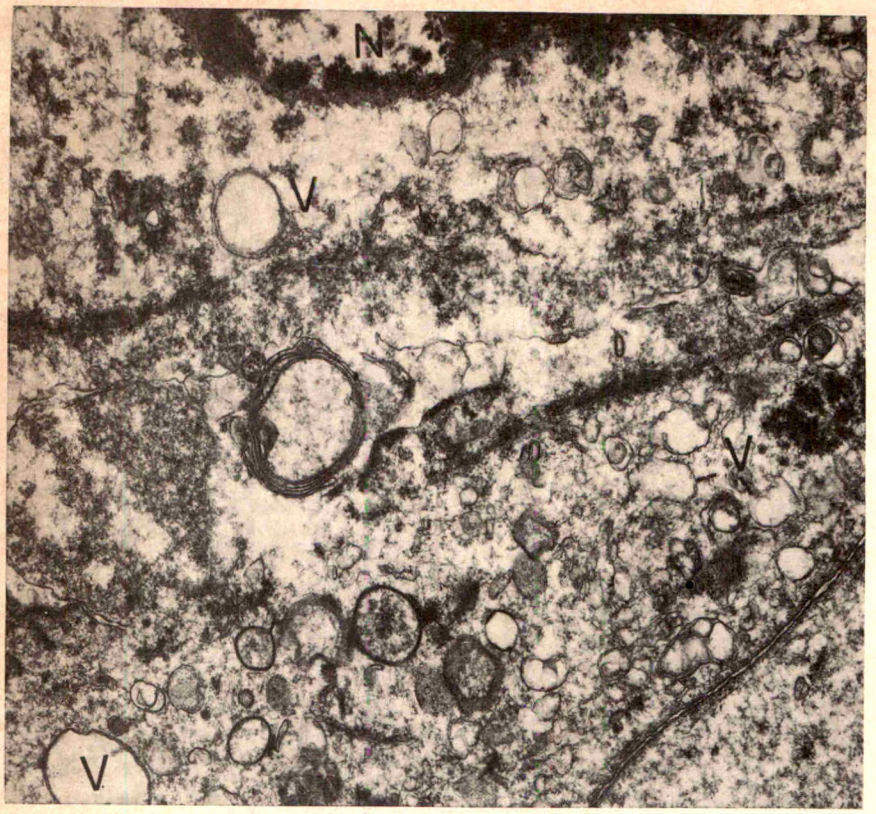
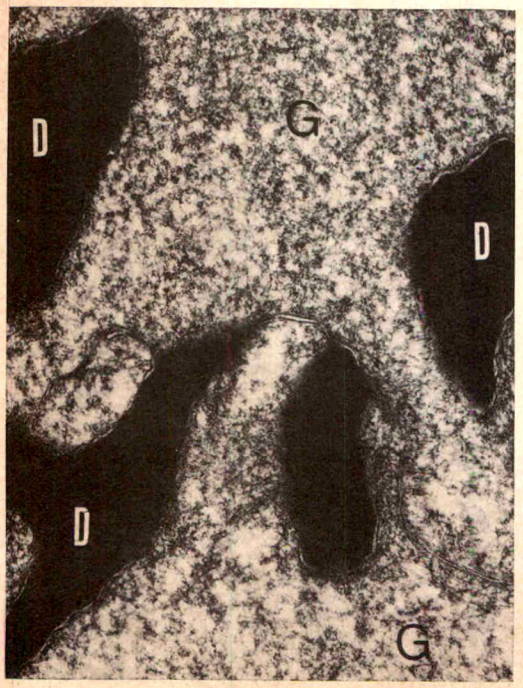
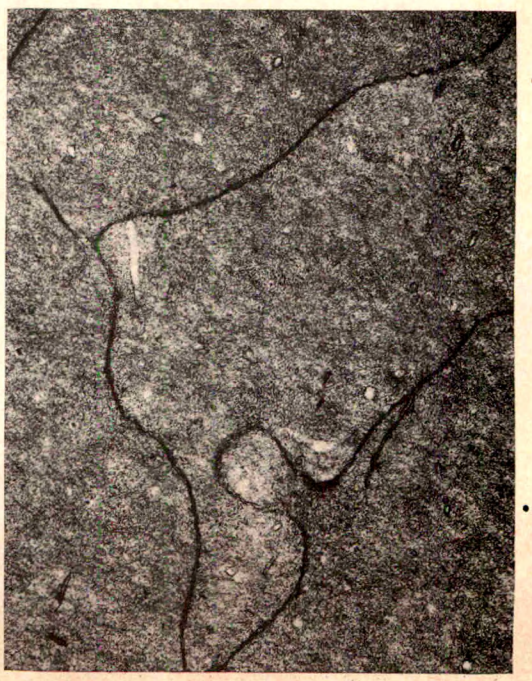
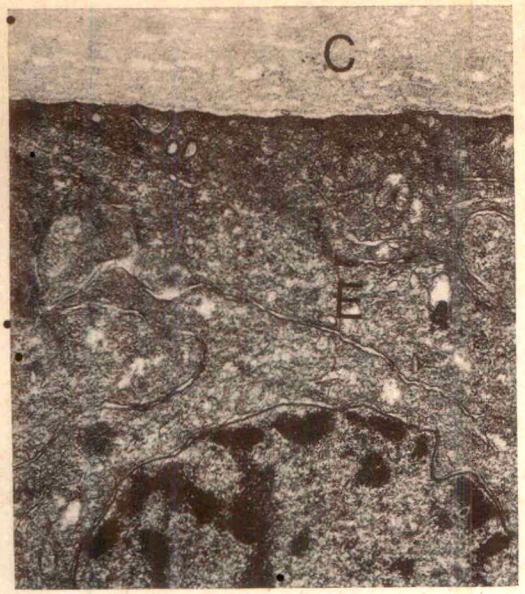


Fig. 4 (Vannas and associates). Equatorial lens cells with many degenerating organelles and clear, fluid-filled vacuoles (V); N indicates nucleus (×13,200).







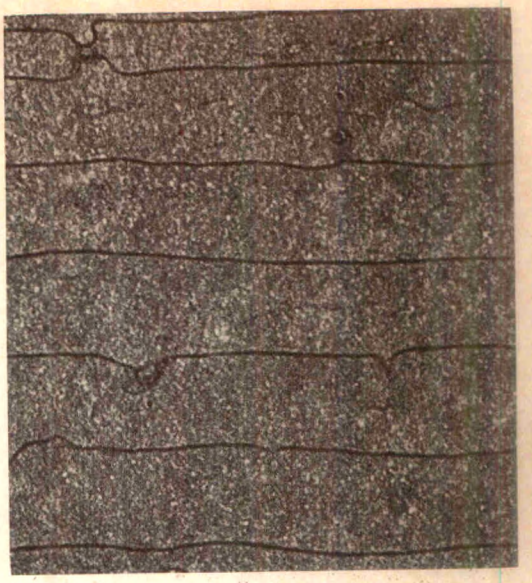




Fig. 6 (Vannas and associates). Top left, Normal eye. Normal anterior capsule (C) and epithelium (E) (×12,600). Top right, Anterior cortex with compact cytoplasm and intact cell membranes (×4,300). Bottom, Normal posterior capsule and cortex (×12,600).

←

Fig. 5 (Vannas and associates). Left, Posterior lens cells. Some have an increased density due to liquefaction and death (D). Others have a loose granular cytoplasm (G), not found in normal cells (×14,600). Right, Posterior cortex near the capsule. The cells show fewer changes than in figure at left. The cytoplasm has some areas of granularity (×14,800).

capsule and epithelial cells were normal (Fig. 6, top left). The epithelial cytoplasm had the normal dense, closely packed, fine granular and fibrillar structure, and the organelles and nuclei were normal. The anterior cortical cells had the normal shape and relationships, without cytoplasmic change (Fig. 6, top right). The posterior capsule and lens also showed no pathologic change (Fig. 6, bottom).

Discussion

Electron microscopy of the lens is fraught with difficulties. Artifacts are frequent and were avoided in this study by the careful processing of both diseased and control tissues. Another source of error can be the presence of a second disease. This is unlikely in connection with galactosemia since the only abnormalities are transient neonatal lens vacuoles.[5] Such vacuoles occur most commonly between eight and 14 days after birth in low-weight babies and persist for only ten to 18 days.[6] Their cause is not known, but they are assumed to be related to a temporary inability of the baby to metabolize carbohydrates when a milk diet is introduced.

Galactose cataracts have been studied in experimental animals fed an excess of galactose. In rats, lens opacities appeared on the third day of feeding, and if galactose was not withheld, the opacities progressed until irreversible, mature cataracts developed in two weeks.[7]

The biochemical events have also been studied. The primary factor in the initiation of the cataract is the high concentration of galactose in the aqueous humor. Galactose is converted into dulcitol, and since the lens membranes are partially impermeable to sugar alcohols, a hypertonicity develops when an abnormal amount of dulcitol accumulates in the lens.[8] Alterations in potassium flux and in the amino-acid concentrating processes also occur early in cataract development. In the lung and liver tissues of the fetus we studied, we measured the concentrations of galactose, galactose 1-phosphate, and hexitol, all of which were elevated; the values were comparable to those observed in children dying of galactosemia. We did not measure the aqueous concentrations of galactose or hexitol, but it is likely that they also were elevated. The conditions needed for galactose-induced cataract were thus present.

The remarkable ultrastructural changes observed in our study were degeneration of the lens epithelial cells as well as intracellular edema, vacuolation, and liquefaction of the lens cells. In experimental animals, changes in the epithelium and edema of the lens cells were early findings,[9,10] with liquefaction of the cells often occurring later. Kuwabara, Kinoshita, and Cogan[9] also described what they considered to be characteristic intercellular cyst formation and edema in the bow region and posterior zone. In our specimen intercellular edema was only minimal, but we do not know whether such edema depends on differing biochemical mechanisms, duration of the process, or on differences between species.

The electron microscopic changes were widespread and corresponded well to the initial or intermediate changes described by Kuwabara, Kinoshita, and Cogan.[9] On gross examination, however, we failed to see any opacities. Possibly we missed some small ones because of the small pupil, the hyaloid artery, and our avoidance of manipulation to prevent artifacts.

It is difficult to say whether the observed electron microscopic changes would have caused visual disturbance in a full-term child. Remission of the lens changes can take place if galactose is excluded from the infant's diet before 3 months of age.[1] On the other hand, the severity of the enzyme deficiency varies widely. In this family one child presumably died from galactosemia, suggesting that the enzyme defect was a severe one, and the biochemical findings in the fetus were corroborative.

This seems to be the first reported case of galactosemia in which lens changes developed by the fifth fetal month, indicating that cat-

aract formation can be demonstrable at birth in some galactosemic infants.

Summary

The first child of a Spanish-American couple died presumably from galactosemia. Early in the mother's fourth pregnancy, the parents' red blood cell levels of galactose 1-phosphate uridyl transferase were measured and both parents were found to be heterozygous (carriers) for transferase deficiency. A prenatal diagnosis of galactosemia in the fetus was made with the aid of amniocentesis and tissue culture. Abortion was induced when the fetus was 5 months old. Biochemical studies of lung and liver tissues confirmed the diagnosis of galactosemia.

Cataractous changes were found by electron microscopy in both fetal eyes. Lens epithelial cells showed degenerative changes and a tendency to proliferate into two cell layers. Edema, liquefaction, and a variation in density characterized the lens cells.

Acknowledgments

We thank Ernest Beutler, M.D., City of Hope National Medical Center, and George H. Donnell, M.D., Children's Hospital of Los Angeles, for performing the biochemical studies.

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A PERIMETRIC TECHNIQUE BELIEVED TO TEST RECEPTIVE FIELD PROPERTIES: SEQUENTIAL EVALUATION IN GLAUCOMA AND OTHER CONDITIONS

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The Westheimer function[1-8] is believed to reflect largely the center-surround receptive field properties of certain retinal neurons.* In a limited area of field immediately surrounding a small flashing test field, increasing the stimulus area of a second or background field results in summation of its visual effect. We call this central area of the second field the "summation arm" of the Westheimer function. When the second field is further increased in diameter beyond the limits of the summation zone, an effect opposite to summation occurs. We call this the "inhibition arm" of the Westheimer function. Under certain test conditions a small additional outer summation-like zone was described.[9] This is not seen when the test is performed as previously described[4,5] and as we did in this study. Beyond such zones the response function asymptotes and no further change in the threshold of the small flashing field occurs. Thus, there is a circumscribed area in the visual field that significantly influences the detectability of a small flashing test field located at its center. Within the circumscribed area there are two response zones, a central summation zone (Fig. 1, SA) and a larger surrounding inhibition-like area.

In diseases of the outer layer of the retina, pigment epithelium, and choroid the entire Westheimer function exhibits reduced sensitivity but its form is not altered. In diseases of the inner layer of the retina, the inhibition arm of the response may be partially or totally eliminated. The distinction between inner and outer retinal layers is tentatively made on the basis of vascular supply (choroidal vs. retinal support). To date we have found no ophthalmic disease that systematically alters the summation arm of the function. Because of its relative stability, the summation arm becomes useful as a reference or "anchor" for the response function. Thus, when looking at a given clinical record of the Westheimer function, one evaluates the sensitivity of the response, that is, one examines (on the graph) the static threshold and determines the vertical position of the summation arm or anchor, then one finds whether the inhibitory arm is present on this test date or has been altered since the last examination. By minimizing retinal image blur at the test point, intersession variance is greatly reduced and inter-observer variability is markedly diminished.[3,4] As a safeguard in testing, a full Westheimer function is initially determined on each patient. If this is within expected bounds and if blur is minimized, one tests only three key points in order to evaluate the Westheimer function at the same point in the visual field on subsequent visits (Fig. 1, B).

When the Westheimer function has been simplified and shortened in the manner just described, it may be used to evaluate a patient's status in time, that is, progression of a disease or the efficacy of therapy can then be evaluated (within the capability of the test). The simplicity of the reduced examination allows the use of routine and noncomplex statistical procedures if desired. Examples of the use of the test for these purposes are included in this study.

If an anomaly exists central to the optic

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*Daw and Enoch[1] extensively studied a patient previously described as a rod monochromat; he actually was a blue-cone monochromat. However, the previous analysis of his measured Westheimer function as being scotopic was valid.

nerve head, it is more difficult to measure the Westheimer function because visual sensitivity tends to fall off markedly in time. This time-dependent loss in sensitivity has been termed a short-term saturation or visual fatigue-like effect. It is evaluated by using the flashing repeat static perimetric test.[2,7,8] This response property (as evaluated by this test) is most useful as a means of localizing the locus of involvement of a disease process.

METHOD

Westheimer function—A psychophysical method was used to define what we believe to be retinal receptive field characteristics by varying the size and luminance of a continuously visible background field upon which was displayed a small, fixed size and luminance, slowly flashing stimulus.

The experiments were conducted by using a Goldmann Haag-Streit perimeter with static and flicker attachments. An added field was introduced and certain limited modifications were made on the equipment.[2-4] Earlier studies more completely summarize the method.[2,4,5,7] These luminous fields are superimposed.

FIELD I—A small, regularly flashing test field (70 msec every 0.5 second) was centered on the point in the visual field to be tested. The just detectable (flashing static) threshold of this small field was first determined against the usual cupola background. The small flashing field was then set at a fixed luminance level above that threshold value (usually between 0.7 and 1.0 log units).[4] The standard pantograph arm on the perimeter provided the flashing test field.

FIELD II—Field II was a background field continuously presented. It was centered about Field I with its area being altered, stepwise, over a large range down to that of Field I.

Either the subject or the examiner varied the luminance of Field II by means of a neutral density filter wedge. The examiner sought to determine when flashing Field I disappeared (by increasing Field II luminance) and then reappeared (by decreasing Field II luminance). Mean values of each of the two sets of measurements of Field II luminance (and ranges of measurements) were plotted for each area (diameter) of Field II. The result comprised the Westheimer function. A modified Haag-Streit fixation projector was employed to form Field II.[2,4,5,7] Luminance of Field II was varied at a rate of 0.1 log unit/second.

FIELD III—The cupola of the Goldmann perimeter formed the surrounding field that we held at the usual luminance value (10.03 candelas/m^2, 31.5 apostilbs, or 3.15 mL) throughout testing. The presence of this field minimized artifactual responses.

The stimulus array was located at 5° on the 0° half meridian or radius on the Goldmann perimeter and an auxiliary fixation projector allowed control of fixation during testing.[4]

When studying lesions causing relative field loss or field loss without sharp boundaries, we selected test loci in areas of relative scotoma. Control data were obtained from (relatively) uninvolved points in the same eye or the fellow eye at the same distance from the fovea.

Flashing repeat static test—The flashing repeat static perimetric test was performed on all patients. The examiner determined the static threshold again and again for a five-minute test period.[2,5,8] First, the patient was given a pretest rest period of three to five minutes with his eyes closed; upon opening his eyes, the test was initiated immediately. The stimulus was adjusted from nonseeing to just seeing at the point in the visual field that was being evaluated. Light adaptation will influence results initially and natural fluctuations in sensitivity will cause some variance in response.[10,11] However, in the normal individual the threshold will vary only modestly during the test period. In the presence of an anomaly central to the optic nerve head, sensitivity tends to fall off sharply within a short period of time. This was termed a short-term saturation or visual fatigue-like effect.[8]

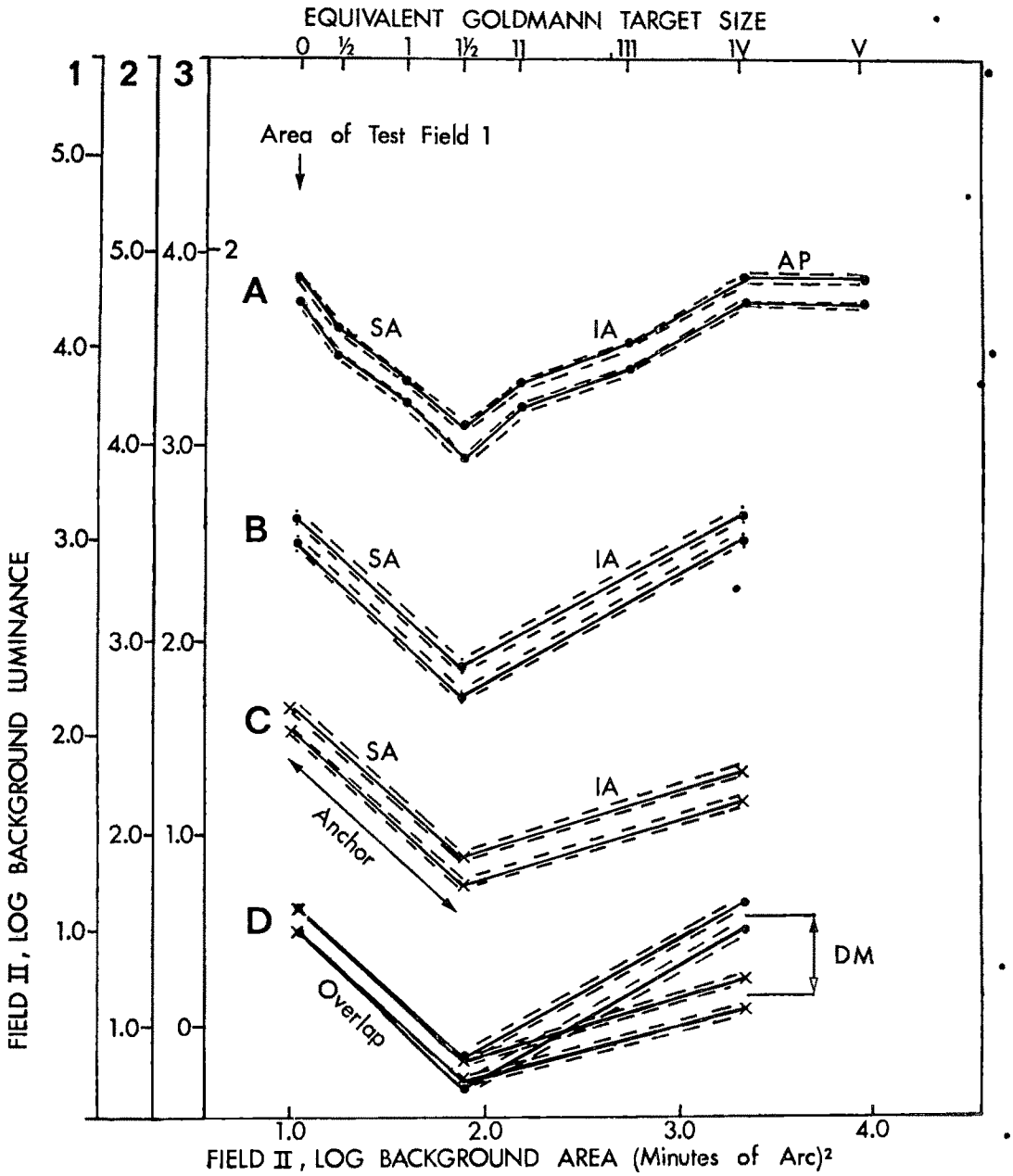


Fig. 1 (Enoch and Lawrence). Case 3. Field II background log luminance is expressed on the ordinate; column 1 is the scale measured in candelas per square meters, column 2 in apostilbs, and column 3 in millilamberts. The specific log luminance value in millilamberts for Figure A is indicated just within the ordinate. SA corresponds to the summation arm of the Westheimer function. IA refers to the inhibition arm, and AP applies to the asymptotic portion of the curve.

A, Westheimer function data for right fovea, on Jan. 2, 1973. Field I luminance was 1.0 log unit above the foveal flashing static threshold. The solid lines indicate the mean data sets; the broken lines give the measurement range for each background size (Field II). B, The points of inflection of the data set in A are reproduced here. C, A hypothetical data set showing the inhibition arm somewhat flattened at a subsequent examination time. D, The anchors (SA) of the two data sets (B and C) were brought into register. One may then compare the two inhibition arms in order to see if a significant change in response has occurred. This is our conclusion because the entire ranges of data for both thresholds no longer overlap. This is a conservative criterion for judgment. The data ranges for the summation arm parts of the figures were not reproduced in order to minimize confusion. DM indicates the difference between the mean thresholds of the two data sets.

Data analysis—The data for a normally shaped Westheimer function (Fig. 1, A) were taken from the right fovea of one patient (Case 3) on Jan. 2, 1973. The size of the flashing test field (Field I) was always equal to or smaller than the size of the smallest steadily presented background field. Two sets of determinations were made for each background field size: flashing test field just invisible, and flashing test field just visible. The solid lines represent the mean and the dotted lines represent the range of the responses for each background size (Field II).

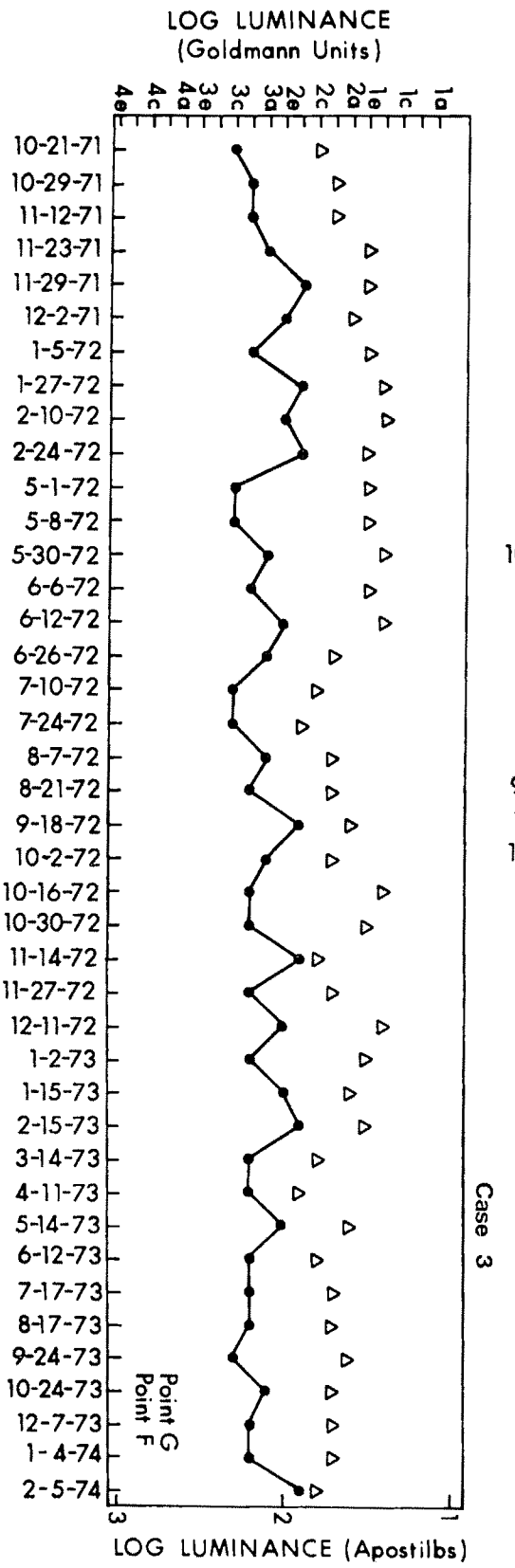
Three key points were selected and connected (solid lines) in Figure 1, B. For practical purposes, these three points define the summation and inhibition arms of the function if blur is minimized at the test points and care is taken in examination. The key information (contained in the determination of the full Westheimer function) is fully expressed by this more limited test sample. This reduced examination time by a factor of more than 2. We assumed that the dimensions of the function do not alter in time. This assumption has been borne out in prior testing. To compare two successive data sets, we made use of the fact that the summation arm is apparently not altered systematically in shape by ocular pathology, that is, while outer retinal layer and choroidal disease may shift the function up and down on the graph, summation arm shape did not appear to be consistently altered. (The upward and downward shift of the function can also be deduced by studying the flashing static perimetric threshold for a small test object at the same test point.) Thus, one may make use of the two sets of test points defining the summation arm to anchor effectively the function for comparison with a second data set.

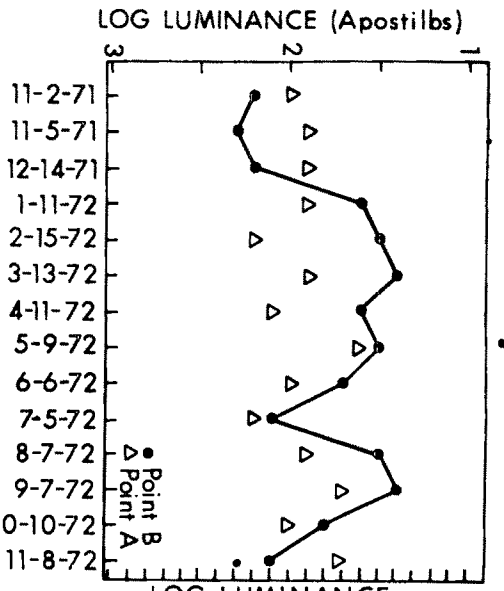
We shifted successive data sets vertically on the graph to obtain the best overlap of the summation arm (SA). The separation of the mean values for flashing test field (Field I) disappearance (upper data set of each pair) and reappearance (lower data set) may not be wholly equal. Similarly, the range of determinations for each judgment may be different. Some variation in slopes also occurs. However, it was not difficult to overlap two data sets satisfactorily (Fig. 1, D). The data sets marked with X's (Fig. 1, C) are hypothetic values for purposes of illustration. The practicality of the approach will be seen.

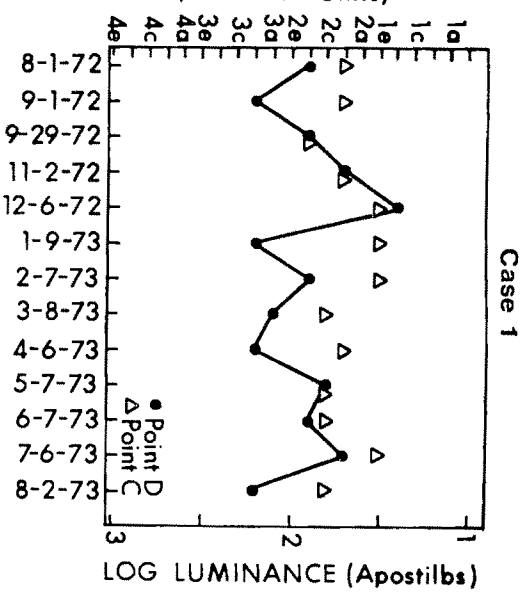
The two sets of curves in Figure 1, D were vertically adjusted so that a common summation arm is shared. If the mean values in the depression (dip) between the two arms of the two data sets are set approximately equal, one can readily determine whether a significant change has occurred in the inhibition arm of the function, that is, one can then ask if the two sets of data taken at the largest test area (right hand values) are the same or different. The null hypothesis can be tested. If the null hypothesis is rejected, a significant change in the inhibition arm has occurred, assuming that our overlapping the summation arms was valid (Fig. 1, D). In a busy practice, routine statistical testing is not practical; a simplified scheme is necessary. In our laboratory a minimum of four pairs of determinations were made at each test point (that is, a minimum of eight determinations) or four for each mean value. The range of each data set is plotted about each mean value. The midpoint between the flashing-field-just-disappeared mean and the flashing-field-just-reappeared mean is regarded as the threshold value. We regard a clinically meaningful change as one in which the two pairs of mean values and two sets of ranges (of the inhibition arm) do not overlap (Fig. 1, D). This is a conservative criterion.

If a question arose as to whether a difference was real or if variance was great, the data set was repeated. We re-evaluated each background area and the function as a whole.

We included three cases in order to demonstrate our techniques. The three subjects were in a double-blind study designed to test the efficacy of diphenylhydantoin sodium (Dilantin sodium) in primary open-angle glaucoma. The question asked in the diphenylhydantoin study was whether this agent helps


LOG LUMINANCE
(Goldmann Units)
4e 4c 4a 3e 3c 3a 2e 2c 2a 1e 1c 1a
10-21-71
10-29-71
11-12-71
11-23-71
11-29-71
12-2-71
1-5-72
1-27-72
2-10-72
2-24-72
5-1-72
5-8-72
5-30-72
6-6-72
6-12-72
6-26-72
7-10-72
7-24-72
8-7-72
8-21-72
9-18-72
10-2-72
10-16-72
10-30-72
11-14-72
11-27-72
12-11-72
1-2-73
1-15-73
2-15-73
3-14-73
4-11-73
5-14-73
6-12-73
7-17-73
8-17-73
9-24-73
10-24-73
12-7-73
1-4-74
2-5-74
Point G
Point F
3 2 1
LOG LUMINANCE (Apostilbs)
Case 3


LOG LUMINANCE (Apostilbs)
3 2 1
11-2-71
11-5-71
12-14-71
1-11-72
2-15-72
3-13-72
4-11-72
5-9-72
6-6-72
7-5-72
8-7-72
9-7-72
10-10-72
11-8-72
Point B
Point A
LOG LUMINANCE
(Goldmann Units)
Case 2


4e 4c 4a 3e 3c 3a 2e 2c 2a 1e 1c 1a
8-1-72
9-1-72
9-29-72
11-2-72
12-6-72
1-9-73
2-7-73
3-8-73
4-6-73
5-7-73
6-7-73
7-6-73
8-2-73
Point D
Point C
3 2 1
LOG LUMINANCE (Apostilbs)
Case 1

protect the function of the neural elements as it does in other anomalies of the central nervous system. (This agent is not meant to aid in the control of intraocular pressure.) The medication was given orally for one six-month period and a symptom equivalent control, phenobarbital, was given during another six-month period. The research team did not know which subject was receiving which drug at any given time. We chose these three subjects for presentation because they had completed the course of testing and because they each illustrated an important point. We had been observing one patient (Case 3) for more than a year before he was admitted to the glaucoma project (Fig. 2).

CASE REPORTS

Case 1—This 72-year-old black man with primary open-angle glaucoma was initially referred to the Glaucoma Center in 1965 because of ocular hypertension; intraocular pressures were R.E.: 20 mm Hg, and L.E.: 32 mm Hg. He had full visual fields and open angles. During the five years he was followed in the Glaucoma Center his intraocular pressures were R.E.: below 20 mm Hg, and L.E.: in the range of 30 mm Hg. There was a suggestion of a nasal step in the left eye as early as 1968. In December 1971, he had a nasal step and a small shallow paracentral scotoma superior and nasal to fixation in his left eye. The nasal defect was not plotted in January 1972; however, it was confirmed in July and the patient was referred to the Dilantin Contract Study. We plotted the visual field of his left eye at the outset of the study (Fig. 3).

There was no history of significant ocular trauma, decreased vision, or ocular surgery. There was no family history of glaucoma.

The patient began the study on Aug. 2, 1972. Physical examination at that time disclosed the following values: visual acuity, 20/20 in both eyes with correction; external examination, motility, and pupils were all within normal limits; slit-lamp examination revealed dense arcus senilis in both eyes with early nuclear sclerosis; gonioscopy revealed grade 2 angles 360°, in both eyes, with no angle recession or peripheral anterior synechia; 24-hour intraocular pressures ranged from 14 to 22 mm Hg (R.E.), and 20 to 26 mm Hg (L.E.); tonography, R.E.: 19.3 with out flow facility of 0.12, and L.E.: 26 with out flow facility of 0.10; and the fundus of the dilated pupil revealed a cup/disk ratio of 0.5 (R.E.), and 0.6 (L.E.). Maculae and vessels in both eyes were normal.

During the study, the patient received no intraocular pressure-lowering medication. Intraocular pressures during the study ranged from 14 to 20 mm Hg (R.E.), and 14 to 29 mm Hg (L.E.) Sequential applanation tonometric determinations are reported in Table 1. Hematologic evaluation, urinalysis, and blood chemistry were all essentially within normal limits. A quantitative VDRL test was nonreactive; however, FTA absorbed was reactive (we do not know whether this patient was treated for syphilis).

Comment—At the outset of the study his left central field (Fig. 3) was normal. We selected two points (C, 15° on 225°; and D. 15° on 45°) for study. These are symmetrically displaced from the fovea and are field areas often showing alteration in glaucoma. An area of relative field loss subsequently developed near point D and we followed changes in the patient's kinetic field in this area and measured his flashing static threshold, his Westheimer function, and his repeat flashing static function* at this point and compared modifications in each indicator of response in time.

The static thresholds of all three subjects are plotted in Figure 2. In all determinations described here, image blur was minimized at the test point. It is obvious that his flashing

* Since the duration of each flash presentation was near the critical duration (70 msec), it is doubtful that the flashing static response differed in a substantial way from a more prolonged test target exposure. The flashing or pulsed stimulus (it is not a "flicker" test) has the advantage of forcing a judgment on each target presentation. It is also useful in discriminating between a loss or alteration of the local adaptation response and a loss due to a short-term saturation or visual fatigue-like factor.

Fig. 2 (Enoch and Lawrence). Flashing static perimetric thresholds at test and control points for the three patients reported during the entire test period. Sequential test point data were connected to minimize confusion. In Case 3, Point G was the test point and Point F was the center point.

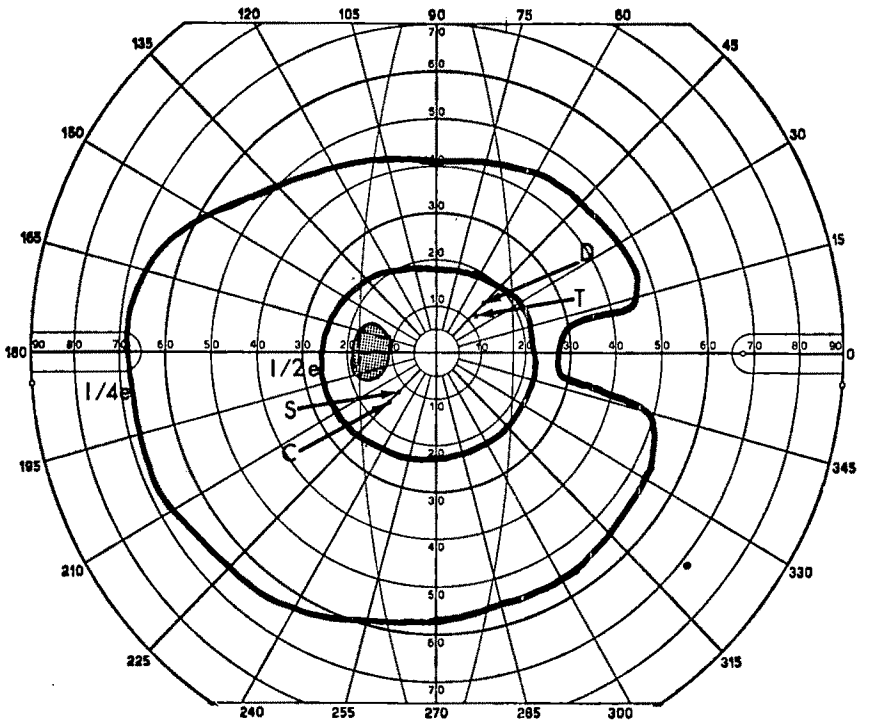


Fig. 3 (Enoch and Lawrence). Case 1, left eye. Kinetic field record at the beginning of the test period. Points D and T were test loci; points C and S were control points.

TABLE 1

APPLANATION TONOMETRY IN CASE 1

Date	Applanation Tonometry, mm Hg		Medication	Westheimer Function	Central Visual Field
	R.E.	L.E.*			
8/2/72	22	26		Normal	Normal
9/1/72	16	24	Contract medication started		
9/29/72	18	27			
11/3/72	20	28			
12/6/72	18	23		Point D, normal; Point T, inhibition arm lost	Deteriorating
1/9/73	10	14			
2/8/73	18	28			
3/8/73	14	19	Contract medication changed	Point D, inhibition arm lost	
4/6/73	20	23			
5/8/73	20	29			Improved
6/7/73	16	24			Vague area
7/6/73	17	19			Slight improvement
8/3/73	17	19	Contract ended		Deteriorating

* Eye described in this paper.

static threshold (Fig. 2, top right) showed some increase in sensitivity at point D, and then a fall in sensitivity at the beginning of 1973. Data at point C (the control point) simply oscillate about Goldmann 2b. Data at subsequent test point T and control point S compare with D and C.

We selected a sample set of this patient's repeat flashing static test data determined at test point T randomly (Fig. 4). His determinations were reasonably stable, suggesting that there was probably no involvement central to the optic nerve head, a typical finding in primary open-angle glaucoma. This set of data was obtained after glaucomatous field changes and alteration in the Westheimer function had occurred.

We compiled a month-by-month determination of his Westheimer function and central field (Fig. 5, parts A and B). In the interest of conserving space, a few fields were deleted, but the trends are evident. The Westheimer function for the control point C (Fig. 5, part A, top) demonstrates an essentially unchanged field throughout.

There was some variation in the Westheimer function from session to session (Fig. 5, part A, point D), but the function remained fundamentally consistent on repetition. We noted kinetic field changes in the area of interest on Dec. 6, 1972, when a relative scotoma developed between point D and the fovea. An additional test and control point were added at that time; these were points T (12° on 44°) and S (12° on 225°) (Figs. 3 and 5, part A). The inhibition arm of the Westheimer function was already flattened at point T, but was normal at control point S (Fig. 5, part C) and at test point D (Fig. 5, part A) on that date. The relative scotoma expanded to include point D and a substantive change in the Westheimer function occurred at this point by March 1973 (Fig. 5, part B). The inhibition arm of the response at point D was lost and did not recover during the test series, although there was a hint of recovery in July. Statistically, however, the latter change may not be significant. The inhibition arm of the Westheimer function at point T remained flattened throughout the balance of the study. Westheimer functions at control points C and S remained virtually unchanged throughout the study.

The static threshold (Fig. 2, upper right) at the points indicated follows the course sug-

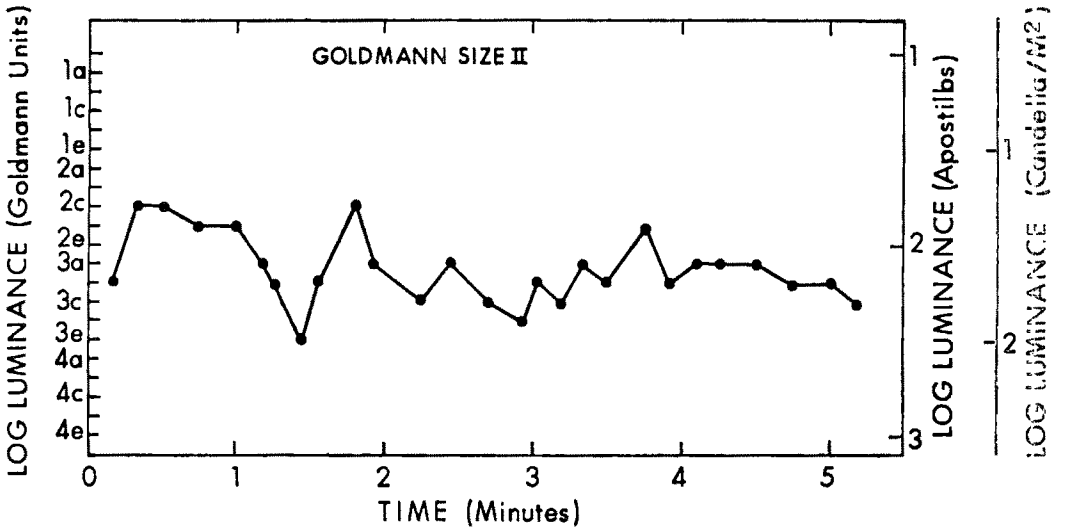


Fig. 4 (Enoch and Lawrence). Case 1, left eye. Flashing repeat static perimetric test data, test point T, Jan. 9, 1973.

TABLE 2

APPLANATION TONOMETRY IN CASE 2

Date	Applanation Tonometry, mm Hg		Medication	Westheimer Function	Central Visual Field
	R.E.*	L.E.			
11/2/71	29	26	Pilocarpine	Point B, inhibition arm lost	Superior defect
12/14/71	29	27	Contract medication started		
1/11/72	24	20			
2/15/72	29	26		Inhibition arm improved	Improved to normal
3/14/72	30	28			
4/11/72	32	30			
5/9/72	28	22			
6/6/72	30	31	Contract medication changed	Inhibition arm deteriorating	
7/5/72	25	25			Deteriorating
8/8/72	29	27		Inhibition arm lost	
9/7/72	33	32			
10/10/72	31	27			
11/9/72	34	35	Contract ended		

* Eye described in this paper.

gested by the kinetic fields in Figure 5, part B. The loss of the inhibition arm of the Westheimer function occurred after initial kinetic field and static threshold changes and did not exhibit significant recovery.

These sets of data provided a unique opportunity to relate the point in time when change in the Westheimer function occurred relative to the change in visual field properties in primary open-angle glaucoma. Different technicians compiled field data and Westheimer function data. The two data sets were joined several months later in all three cases except for those obtained during the first treatment regimen in Case 3 where the same person (B.L.) obtained all data.

Case 2—This 70-year-old black woman with primary open-angle glaucoma in her right eye joined the study in November 1971.

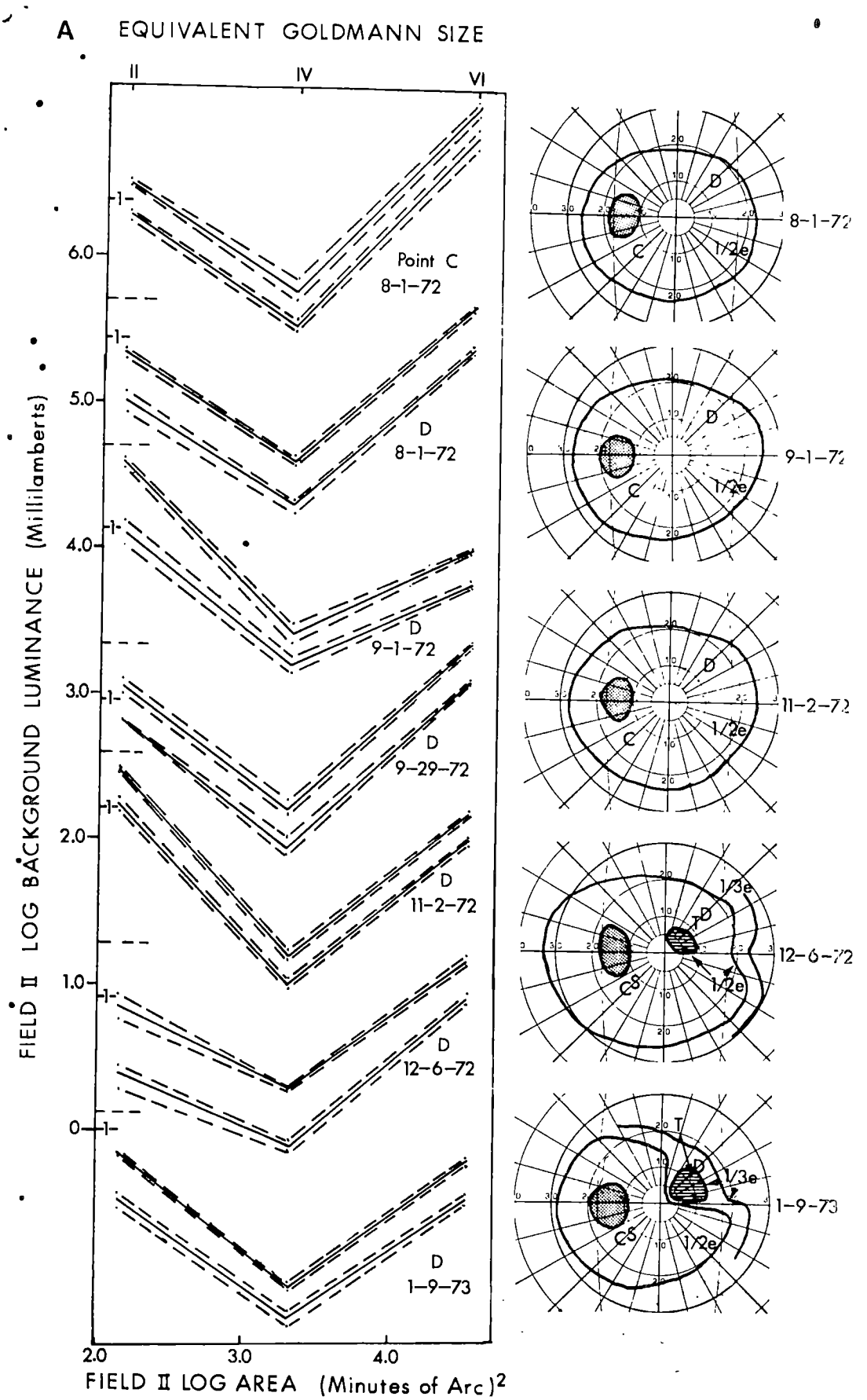
Her past ocular history was noncontributory. There was no ocular pain, redness, halos, or round lights. A daughter and a son had primary open-angle glaucoma.

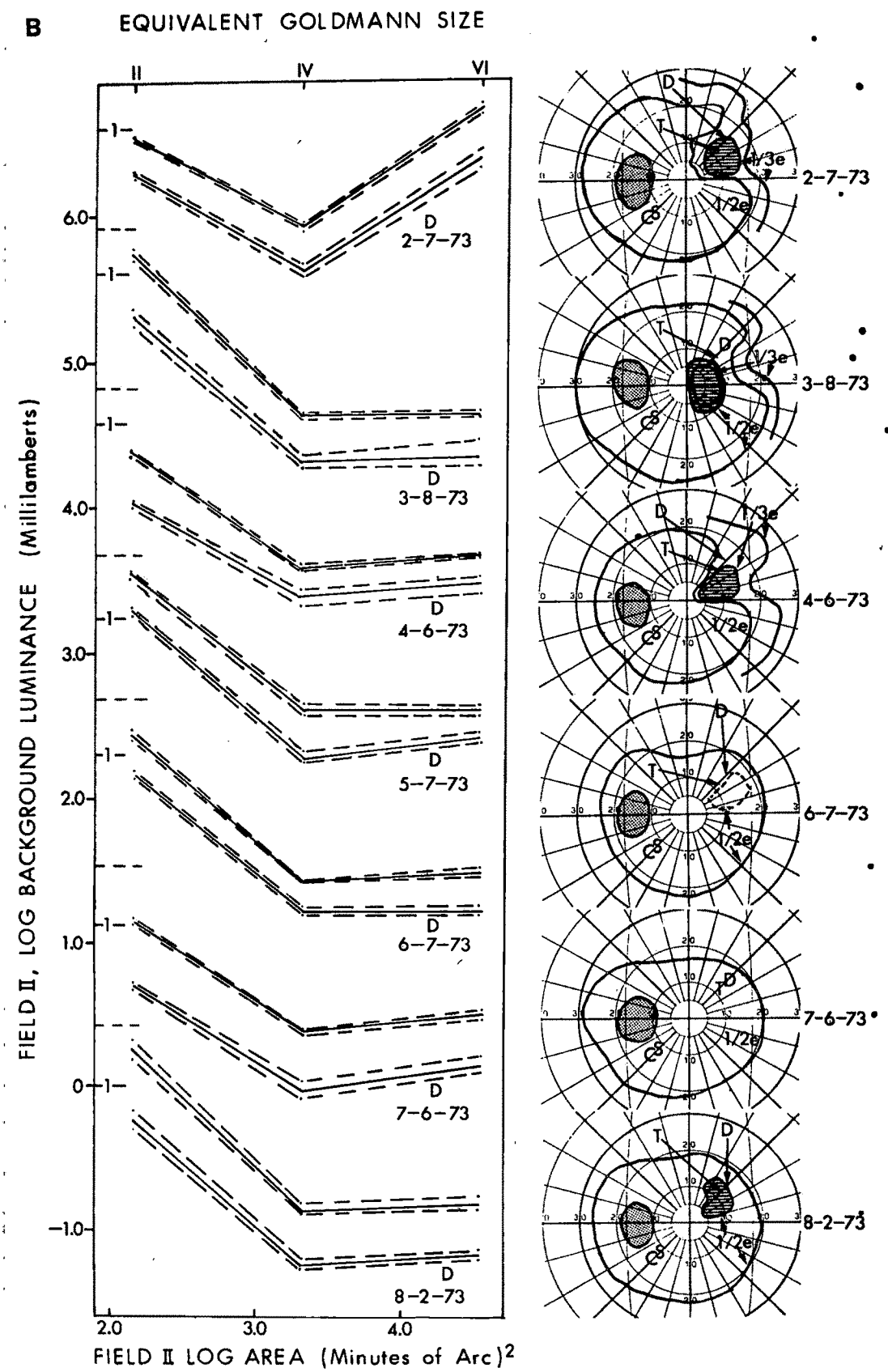
Her ocular examination included the following values: visual acuity was 20/25+, in both eyes; external examination, motility, and pupils were within normal limits; slit-lamp examination revealed mild nuclear sclerosis of both eye lenses; gonioscopy revealed grade 1 to 2 angles 360°, in both eyes, with repeated negative dilation provocative tests; fundus revealed a 0.7 cup/disk ratio with normal maculae and vessels; 24-hour intraocular pressures ranged from 22 to 33 mm Hg (R.E.), and 20 to 30 mm Hg (L.E.); tonography, R.E.: 30.4 with outflow facility of 0.25, and L.E.: 24.8 with outflow facility of 0.17.

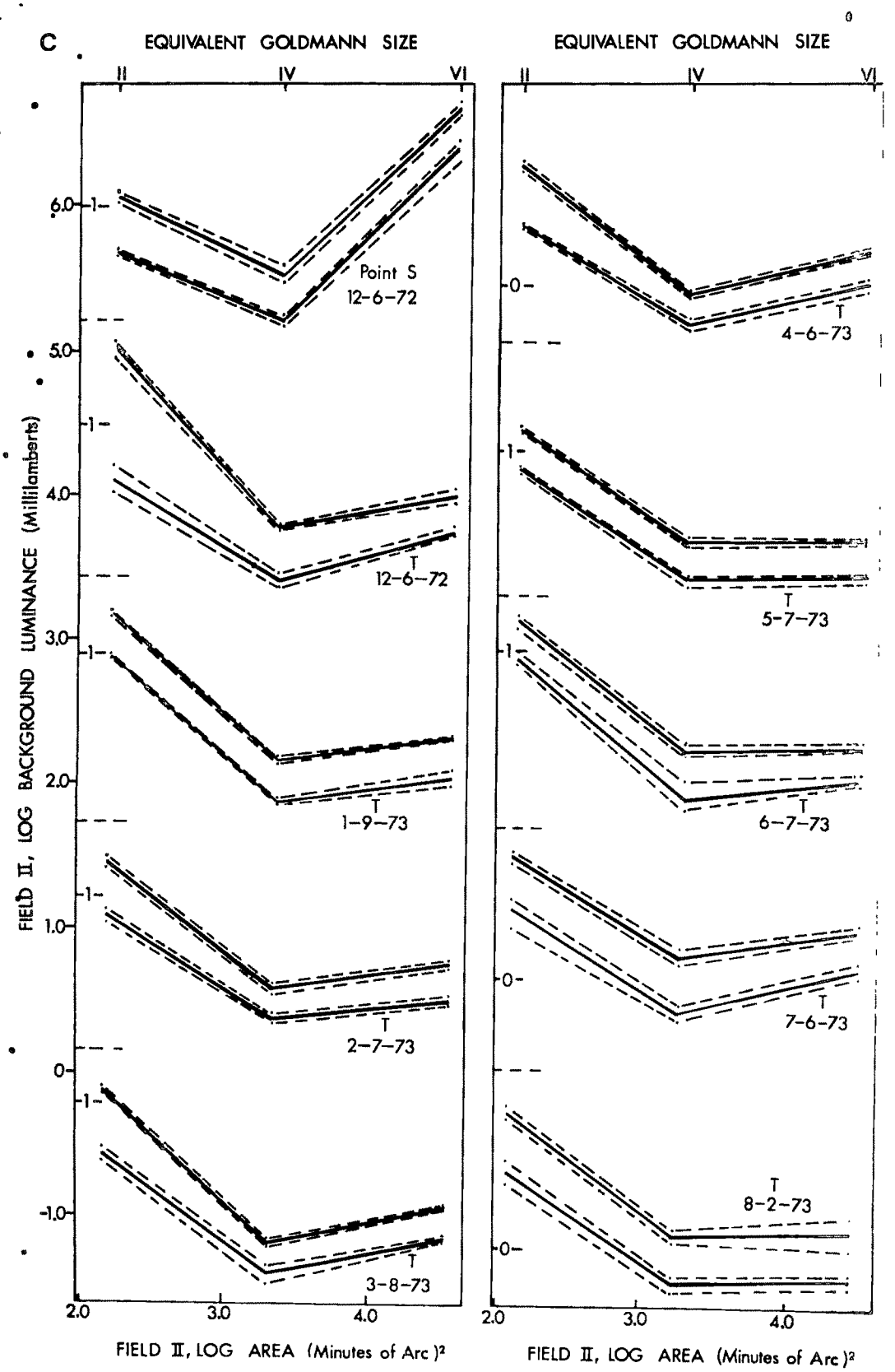
The patient received pilocarpine 4% in both

Fig. 5 (Enoch and Lawrence). Case 1. Sequential Westheimer functions with several parallel central kinetic field records obtained at approximately the same time. A, the top left Westheimer function data set refers to the control point C; all other Westheimer function data on parts A and B refer to test point D. An additional test (T) and control point (S) were added to the experiment on Dec. 6, 1972. Westheimer functions obtained at these two loci are shown in part C with the upper left data set referring to control point S and all other data referring to test point T. Stippled (or dotted) areas on the field represent the blind spot (I_2e unless otherwise designated). Horizontal line patterns signify areas of relative scotoma.

The Field II background log luminance scale (millilamberts) to the left of the Westheimer functions is not specific for any data set: the scale applies to the entire chart. Specific values for each data set are designated just within the ordinate. Horizontal dashed lines, also present just within the ordinate, separate the specific luminance values measured on the different dates.


A EQUIVALENT GOLDMANN SIZE
II
IV
VI
Point C
8-1-72
D
8-1-72
D
9-1-72
D
9-29-72
D
11-2-72
D
12-6-72
D
1-9-73
6.0
5.0
4.0
3.0
2.0
1.0
0
FIELD II LOG BACKGROUND LUMINANCE (Millilamberts)
2.0
3.0
4.0
FIELD II LOG AREA (Minutes of Arc)²
D
C
1/2e
8-1-72
D
C
1/2e
9-1-72
D
C
1/2e
11-2-72
1/3e
T
D
CS
1/2e
12-6-72
T
D
1/3e
CS
1/2e
1-9-73


B
EQUIVALENT GOLDMANN SIZE
II
IV
VI
FIELD II, LOG BACKGROUND LUMINANCE (Millilamberts)
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
D
2-7-73
3-8-73
4-6-73
5-7-73
6-7-73
7-6-73
8-2-73
2.0
3.0
4.0
FIELD II LOG AREA (Minutes of Arc)²
T
CS
1/3e
1/2e


C
EQUIVALENT GOLDMANN SIZE
II
IV
VI
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
Point S
12-6-72
T
12-6-72
T
1-9-73
T
2-7-73
T
3-8-73
FIELD II, LOG BACKGROUND LUMINANCE (Millilamberts)
2.0
3.0
4.0
FIELD II, LOG AREA (Minutes of Arc)²
EQUIVALENT GOLDMANN SIZE
II
IV
VI
T
4-6-73
T
5-7-73
T
6-7-73
T
7-6-73
T
8-2-73
2.0
3.0
4.0
FIELD II, LOG AREA (Minutes of Arc)²

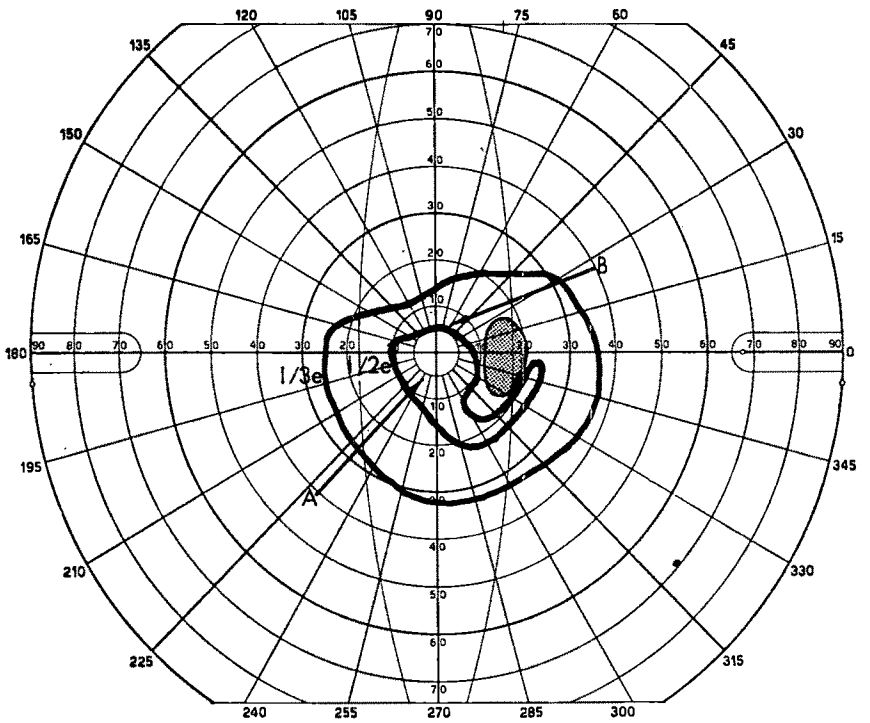


Fig. 6 (Enoch and Lawrence). Case 2, right eye. Kinetic visual field record at the beginning of the test period. Point B was the test point and point A was chosen as control point for this test series, Nov. 2, 1971.

eyes, four times daily, throughout the year of the study.

Intraocular pressures ranged from 24 to 37 mm Hg (R.E.), and 20 to 37 mm Hg (L.E.) during the year of the study. Sequential applanation tonometric determinations are listed in Table 2.

Hemotologic evaluation showed a mild leukopenia. Urinalysis was within normal limits; blood chemistry showed an elevated cholesterol level and abnormal glucose tolerance test. Skull and optic foramena x-ray films were within normal limits.

Comment—The primary open-angle glaucomatous field loss was fairly well advanced in the right eye (Fig. 6) at the outset of the study. Point A (7° on 240°) was the control test point and point B (7° on 60°), located in an area of relative field loss, served as the test point. Her kinetic field, static threshold, and Westheimer function improved during the first six-month period while the improvement in her visual field and other responses regressed during the second six-month period. Her situation can best be appreciated by following her kinetic field (Fig. 7), which started to improve almost immediately. The field recorded by the technician on Jan. 11, 1972, is odd. Her condition exacerbated according to the field on July 5, with the situation deteriorating from that time onward. She changed medication after May 11. Her flashing static threshold (Fig. 2, upper left) roughly follows the kinetic field course, although sensitivity on Aug. 7 and Sept. 7, seems disproportionately high. (Fortunately, control point A was in an area largely unaffected by the fluctuations in the field.)

With practice, the patient's Westheimer function (Fig. 7) measurement ranges narrowed (compare Dec. 14, 1971, with Sept. 7, 1972). The Westheimer function improved on Feb. 15; this improvement lasted until May or June. We observed a steady decline in the inhibition arm from that time. The changes in the Westheimer function seemed

to be lagging the kinetic field changes less in Case 2 than in Case 1. In Case 2, transient reversal of inhibition arm loss was unequivocally demonstrated in glaucoma. This underscored the reversibility of these changes up to a certain point in the progression of the disease. Her repeat static finding remained relatively stable throughout (Fig. 8).

Case 3—This 56-year-old black man, referred to the Glaucoma Center with the probable diagnosis of tobacco-alcohol amblyopia and questionable glaucoma, had a six-year history of difficulty with both distance and near vision. He had progressive loss of both visual acuity, greater in his left eye, and color vision, in both eyes. He supposedly had 20/20 vision, in both eyes, and normal color vision in the Armed Forces.

The patient had a history of heavy alcoholic intake "whenever he gets the money." He denied DT's, seizures, drinking moonshine, or illegal alcoholic beverages. The patient did not have a contributory history of exposure to other toxins. He had smoked one half to one package of cigarettes per day for many years.

A Farnsworth 100-hue test Oct. 19, 1971, revealed poor hue discrimination, typically seen in individuals with a history of alcoholism. There seemed to be a slight tendency toward the deutan axis.

The patient had repeated injections of hydroxocobalamin, during 1972. He had been treated for syphilis and had a positive FTA Abs with a negative cerebrospinal fluid VDRL test. The patient began the Dilantin study in February 1973. At that time, ocular examination values were as follows: visual acuity (Fig. 9); fundus (dilated) revealed a 0.8 cup/disk ratio (R.E.), and 0.7 cup/disk ratio (L.E.) with normal maculae and vessels; slit-lamp examination was unremarkable; 24-hour intraocular pressures ranged from 19 to 40 mm Hg (R.E.), and 19 to 22 mm Hg (L.E.) while receiving pilocarpine 4%, four times daily, and epinephrine hydrochloride (Glaucon) 2%, twice a day, to his right eye; tonography, R.E.: 22 with outflow facility of 0.32, and L.E.: 22 with outflow facility of 0.25.

The year of the diphenylhydantoin study, the patient received the following medication to the right eye: pilocarpine 4%, four times daily, epinephrine hydrochloride 2%, twice a day; and Contract medication.

Intraocular pressures during the study ranged from 15 to 33 mm Hg (R.E.) and 17 to 36 mm Hg (L.E.). Sequential applanation tonometric determinations are reported in Table 3.

The patient was somewhat unreliable in taking his medications. We did not note progression in disk cupping during the year of the study. Hematologic evaluation, blood chemistry, and urinalysis were within normal limits.

Comment—This case was complex. There was evidence of prior syphilitic involvement and the presence of tobacco-alcohol amblyopia and primary open-angle glaucoma. Throughout our study, there were some fluctuations in his responses; he repeatedly returned to alcohol but was cooperative at most test sessions. There were two therapeutic periods: during the first course he was treated with hydroxocobalamin for his tobacco-alcohol amblyopia, and during the second treatment period he was included in the diphenylhydantoin evaluation study.

We examined the patient initially in our laboratory on Oct. 17, 21, and 29, 1971. At that time he had substantial field loss. His kinetic field on Oct. 29, is shown in Figure 10. Test data were taken repeatedly in an area of relative field loss (point G, 12° on 128°) and an area of essentially normal response (point F, 12° on 217°) located at the same distance from the fovea as point G. Data on foveal response were also assembled (Fig. 1, A). At the outset, his right visual acuity was poor (Fig. 9) and the inhibition arm of the Westheimer function in the fovea was somewhat flattened. Fixation was good. The flashing repeat static (Fig. 11) at the control point F (Fig. 10) remained relatively stable. However, the flashing repeat static at test point G (Fig. 12), exhibited a decline in sensitivity in time, typical of a short-term saturation or visual fatigue-like effect. This signified involvement central to the optic nerve head.[8] At the same time his Westheimer function[7] (Fig. 13, part A) showed a loss of the inhibition arm at point G, but normal form at control point F; this indicated inner retinal involvement as well. On Oct. 21, 1971, point G had lower sensitivity (0.5 log unit) than point F on the flashing static test (Fig. 2). It would be valuable to know if the outer retinal layer was involved (a local electroretinogram would aid in such a decision). Foveally, the inner retinal layer was probably involved to a lesser degree.

We began treating the tobacco-alcohol amblyopia on Oct. 29, 1971, with a series of 17 intramuscular injections of 1,000 µg

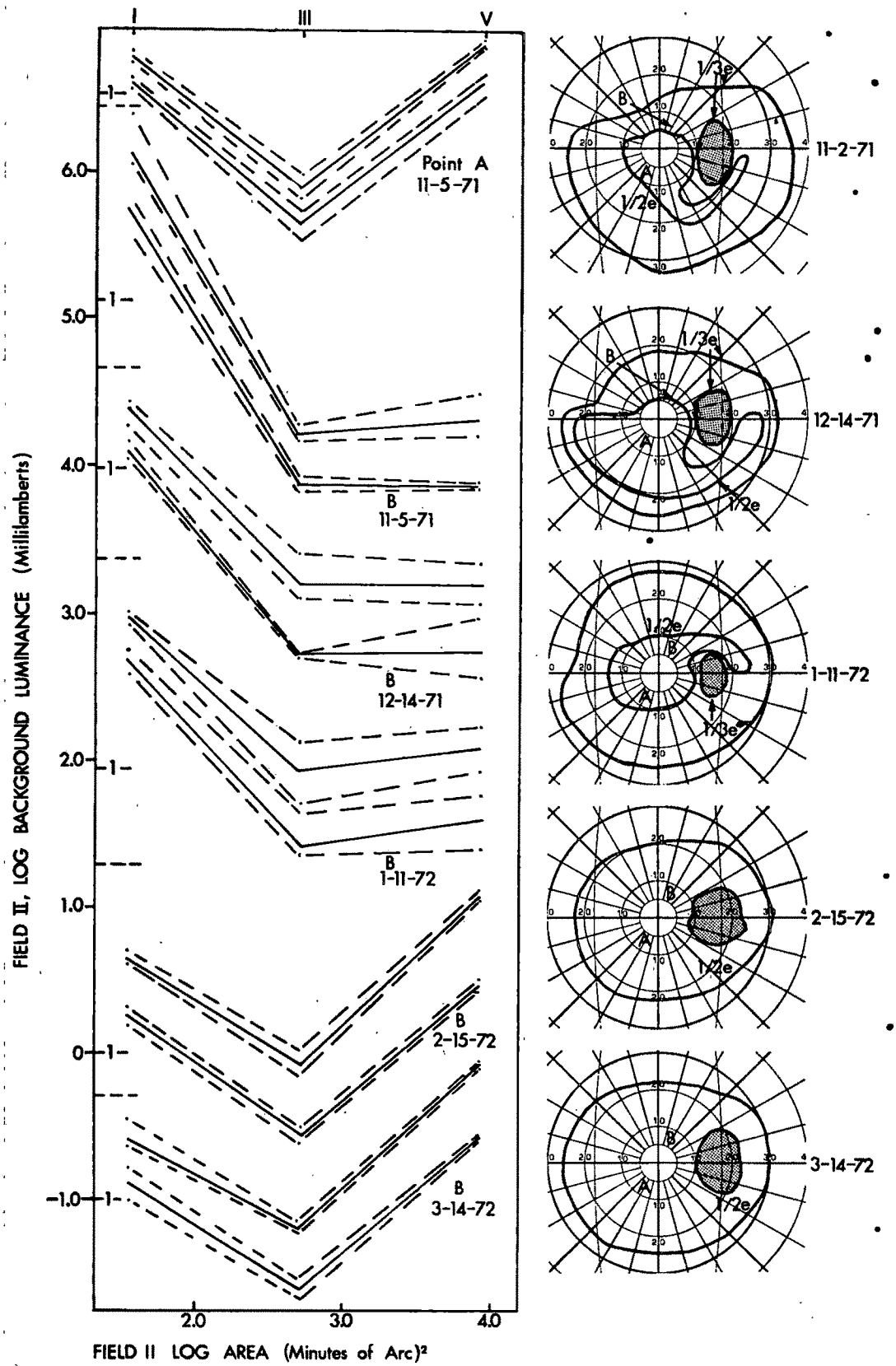
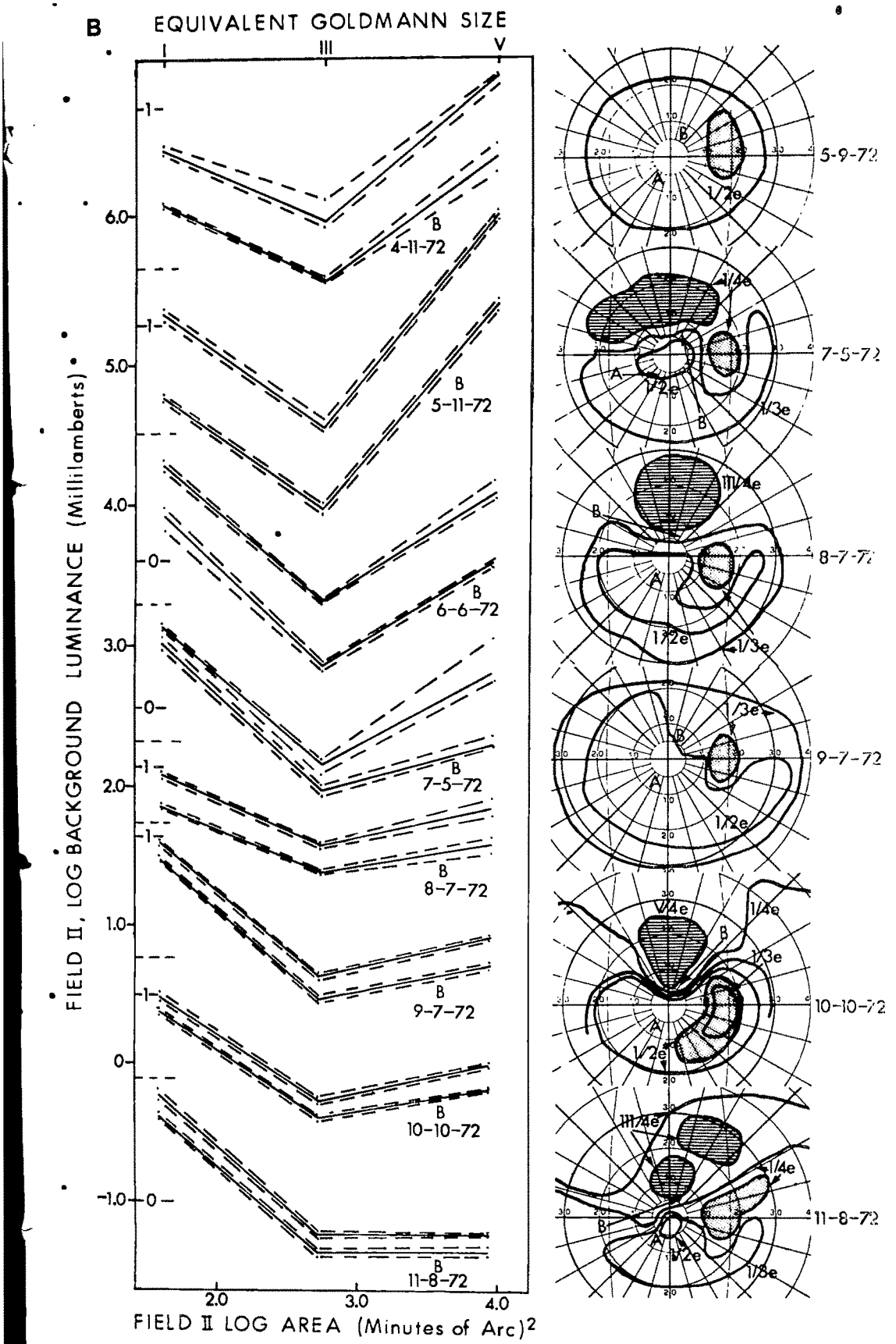


Fig. 7 (Enoch and Lawrence). Case 2, right eye. Sequential Westheimer function data with several parallel central kinetic field records obtained at approximately the same time. The upper left data set (part



The stippled or dotted areas on fields represent the blind spot (I₂e unless otherwise designated). T

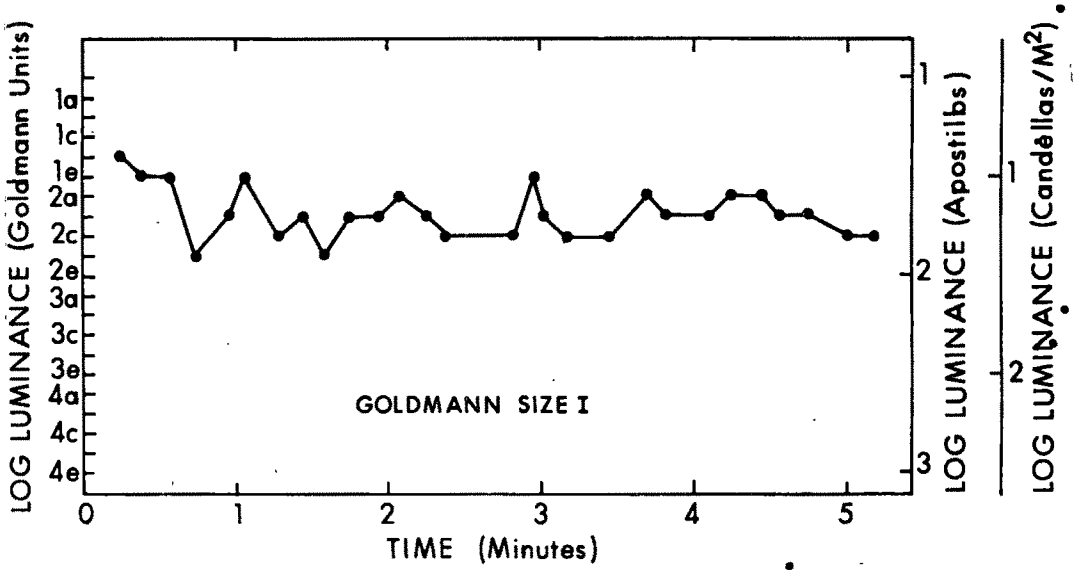


Fig. 8 (Enoch and Lawrence). Case 2, right eye. Flashing repeat static perimetric test data, test point B, Sept. 7, 1972.

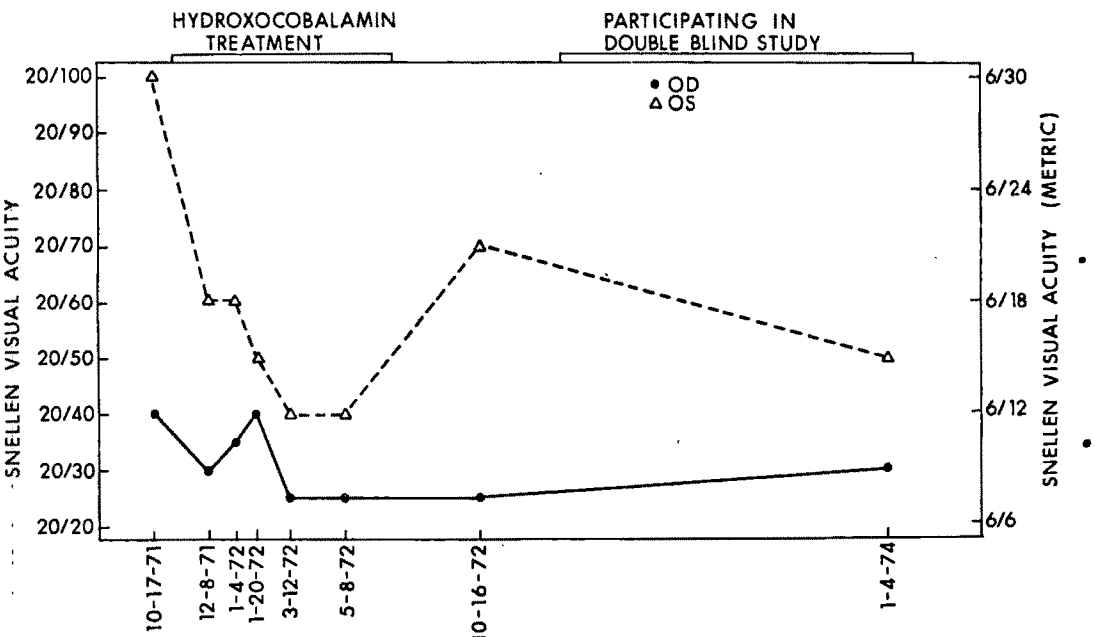


Fig. 9 (Enoch and Lawrence). Case 3. Foveal visual acuity determinations made at different times with optimal refractive correction. The time scale on the abscissa was made approximately linear. Periods of special treatment are indicated on the top of the figure.

hydroxocobalamin (Vitamin B12b) at approximately two-week intervals. Little change was noted after the first injection, or immediately after the second injection. However, between the second and third injections dramatic improvements were recorded in all response parameters. The improvement in the Goldmann I'_3e kinetic perimetric isopter occurred on Dec. 8 (Fig. 14). The visual saturation or fatigue-like effect previously observed on the flashing repeat static test (Fig. 12, a-c) was no longer present (Fig. 12, D). On Nov. 23, the inhibition arm of the Westheimer function showed marked recovery (Fig. 13, part A). Foveal Westheimer function data took on a relatively normal appearance that was sustained. At that time, flashing static thresholds at both points F and G also showed improvement (Fig. 2). Visual acuity improved in both eyes by Dec. 8 (Fig. 9). Most functions showed continued or sustained improvement throughout the course of treatment except the Westheimer function at point G (Fig. 13, A, bottom), and the static threshold (Fig. 2). We initially noted deterioration in these functions on April 4, 1972. The field determined on May 30, showed some deterioration near test point G.

After termination of the hydroxocobalamin treatment on June 26, the fate of the various parameters varied. The flashing repeat static test at point G remained relatively steady

TABLE 3

APPLANATION TONOMETRY IN CASE 3

Date	Applanation Tonometry, mm Hg		Medication	Westheimer Function	Central Visual Field
	R.E.*	L.E.			
10/18/71	35	21	Hydroxocobalamin started 10/29/71	Point G, inhibition arm lost	Superior defect
12/8/71	32	26		Inhibition arm improved	Improved
1/4/72	21	21			
3/2/72	33	19			
3/16/72	31	20			
3/30/72	39	26	Pilocarpine started		
4/6/72	33	21			
4/11/72	27	22			
4/18/72	17	17			
5/3/72	25	21	Epinephrine hydrochloride started	Inhibition arm deteriorating	Deteriorating
6/1/72	27	19			
7/11/72	19	17	Hydroxocobalamin ended 6/26/72	Inhibition arm lost	
10/9/72	21	20			
1/8/73	29	26			
1/16/73	19	19	Contract medication started		
2/15/73	32	22			
3/14/73	22	24			
4/12/73	16	18			
5/14/73	19	19			Slight improvement
6/12/73	22	22			
7/18/73	28	24	Contract medication changed		
8/17/73	23	20			Deteriorating
9/24/73	28	19			
10/25/73	29	19			
12/7/73	20	17			
1/4/74	33	36			
2/5/74	19	17	Contract ended		

* Eye described in this paper.

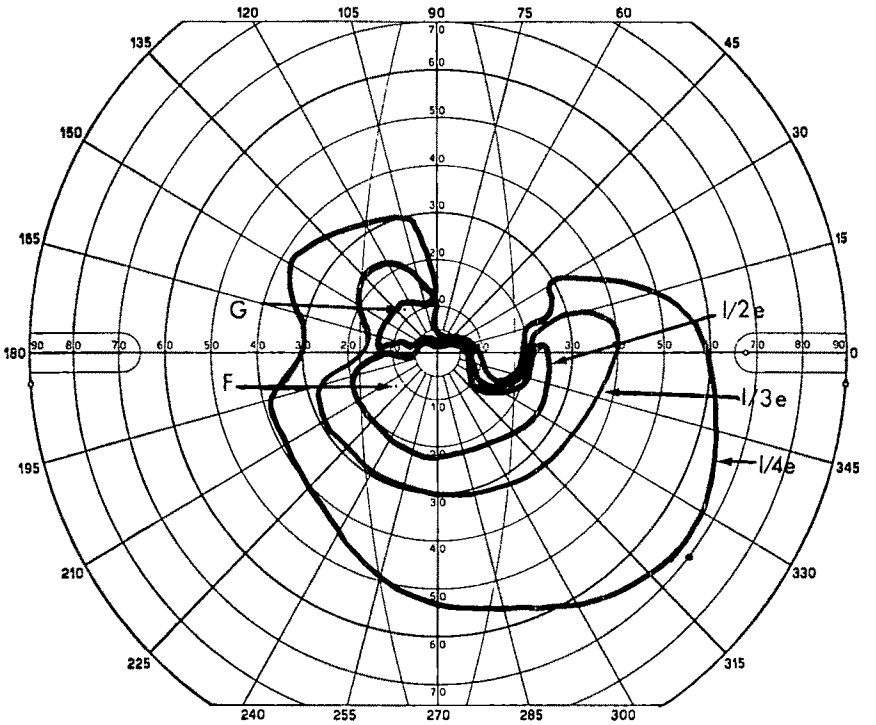


Fig. 10 (Enoch and Lawrence). Case 3, right eye. Kinetic visual field record at the outset of the test sequence. Point G is the test point, point F the control point, Oct. 29, 1971.

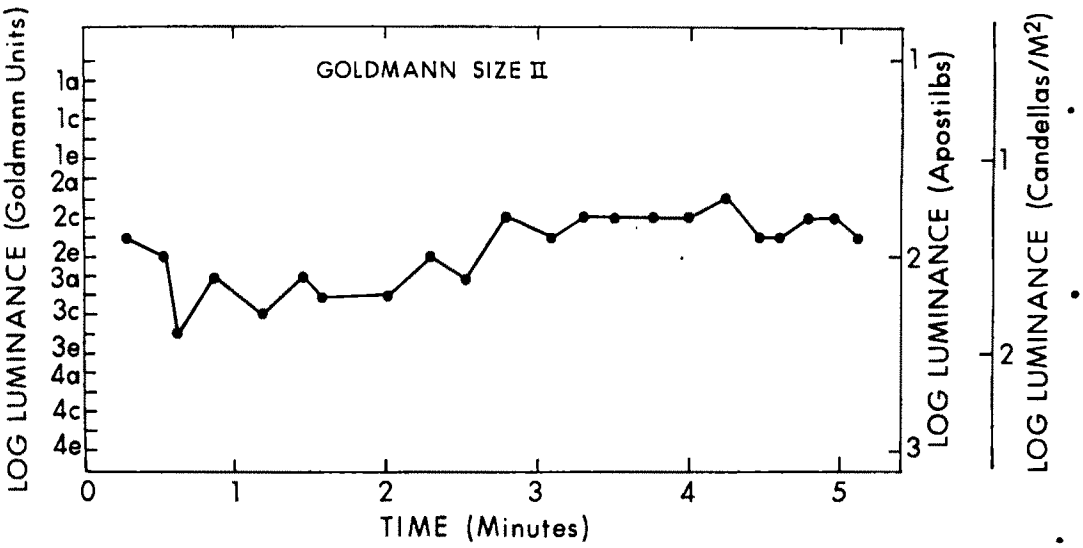


Fig. 11 (Enoch and Lawrence). Case 3. Flashing repeat static perimetric test data at the control point F on Oct. 21, 1971. At this time, the flashing repeat static test revealed a short-term saturation or visual fatigue-like effect at the test point G (see Figure 12).

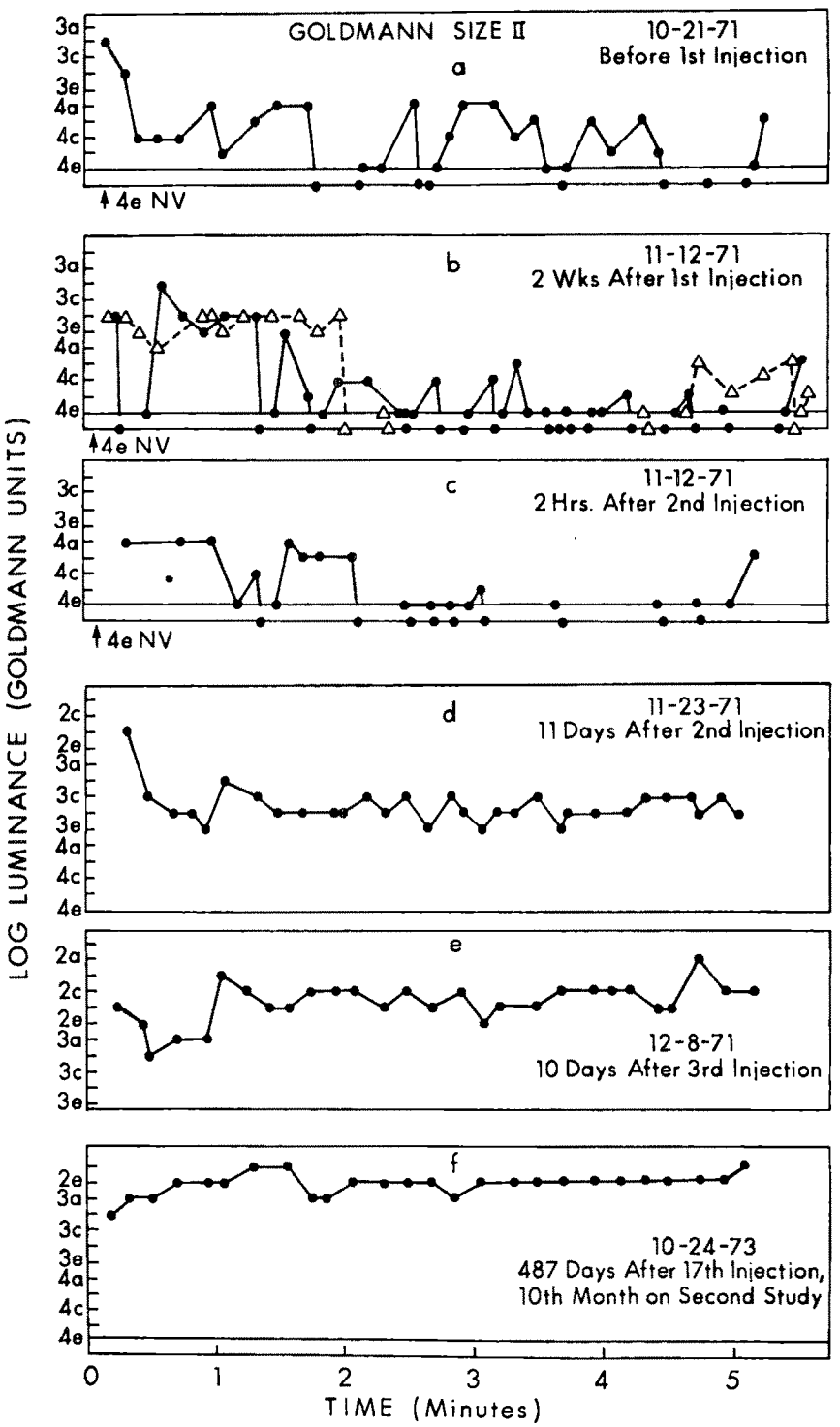
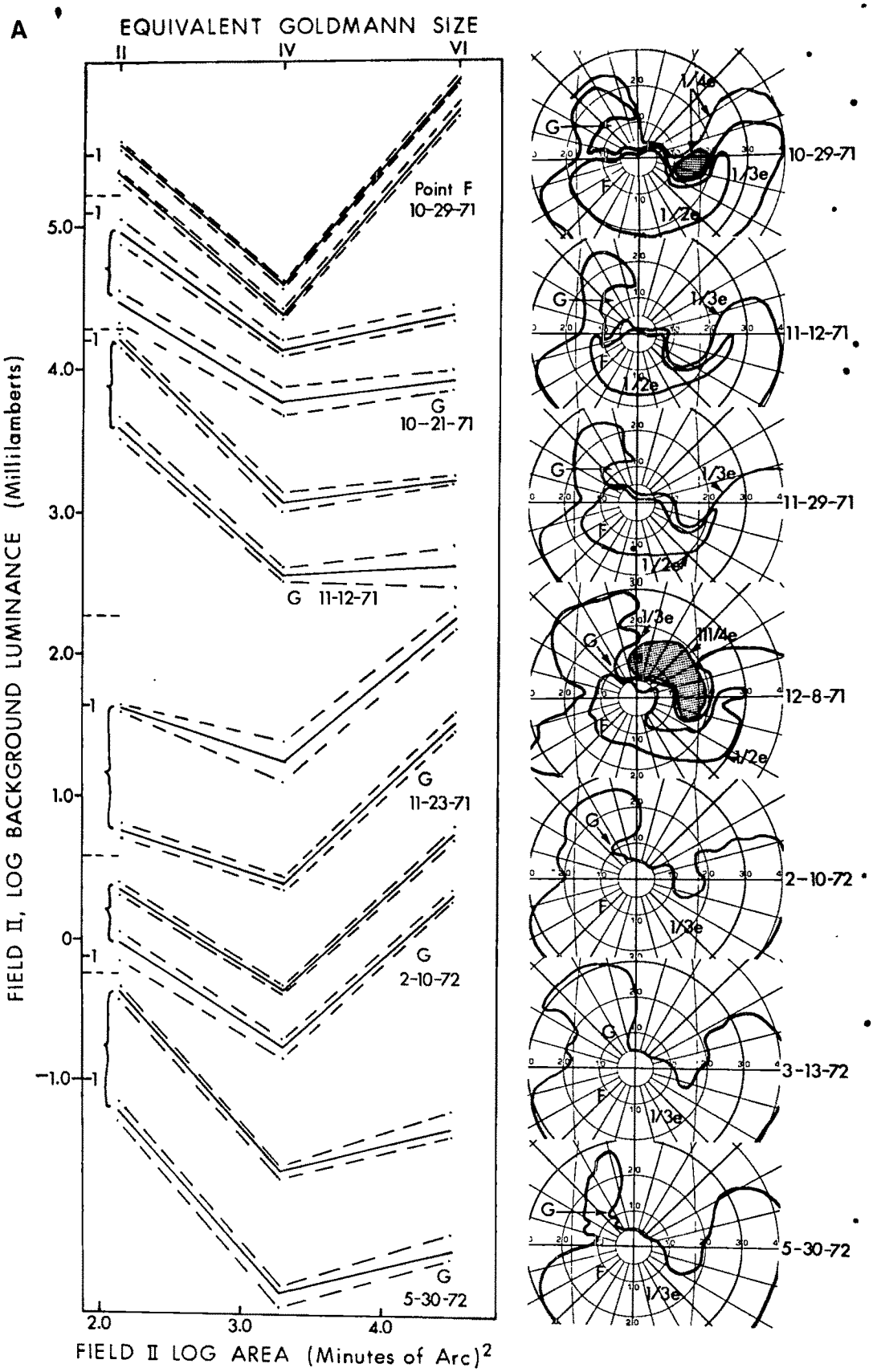


Fig. 12 (Enoch and Lawrence). Case 3. Sequential flashing repeat static perimetric test data at test point G. In b, the open triangles indicate retest response after a brief rest period. In a, b, and c, the symbols on line 4eNV indicate that the stimulus was not visible. In c and d, note the dramatic recovery between the second and third injection of hydroxocobalamin. This improvement was sustained.


A
EQUIVALENT GOLDMANN SIZE
II
IV
VI
Point F
10-29-71
G
10-21-71
G 11-12-71
G
11-23-71
G
2-10-72
G
5-30-72
5.0
4.0
3.0
2.0
1.0
0
-1.0
FIELD II, LOG BACKGROUND LUMINANCE (Millilamberts)
2.0
3.0
4.0
FIELD II LOG AREA (Minutes of Arc)²
1/4e
1/3e
1/2e
10-29-71
11-12-71
11-29-71
12-8-71
2-10-72
3-13-72
5-30-72

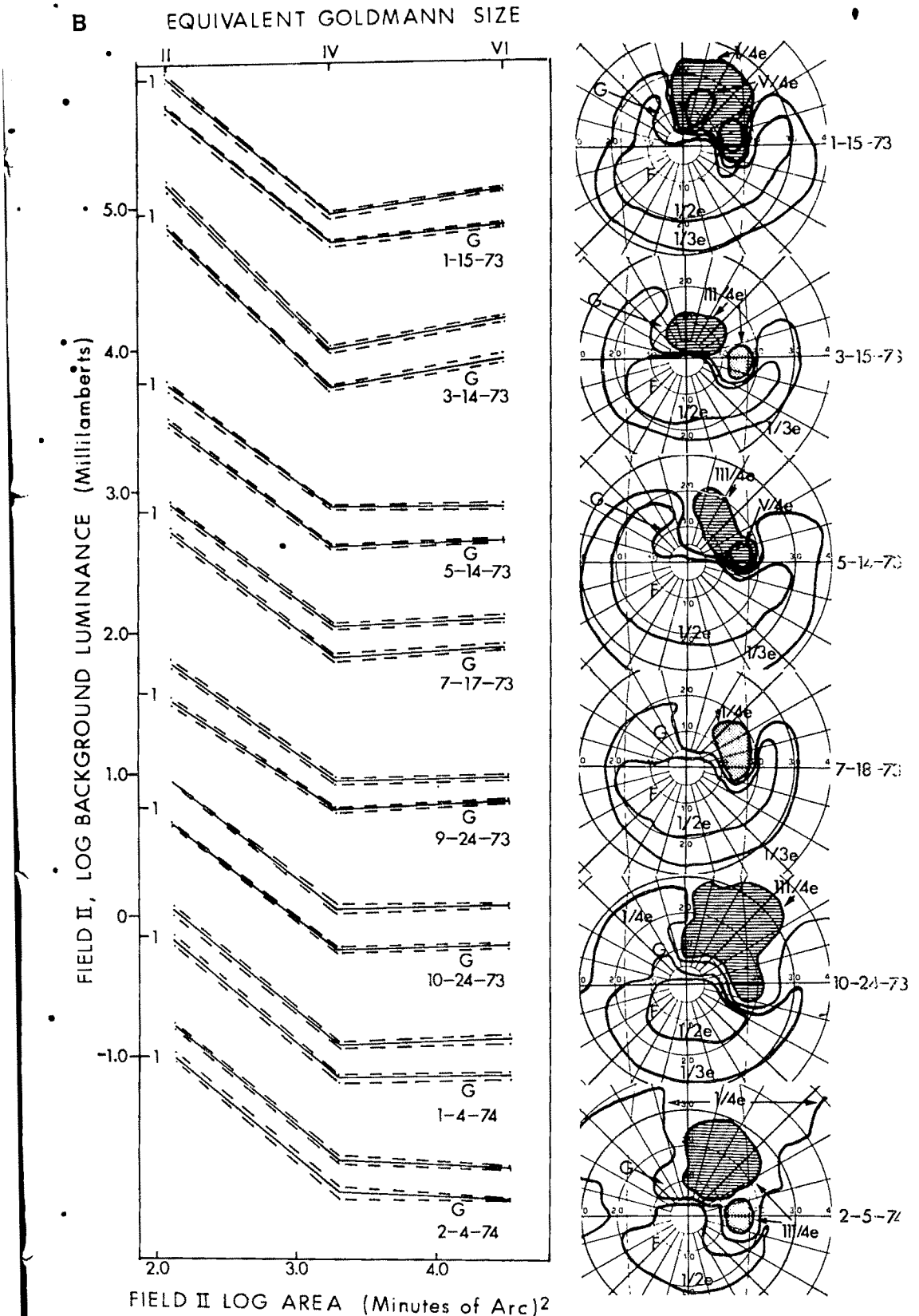


Fig. 13 (Enoch and Lawrence). Case 3, right eye. Sequential Westheimer function test data wi several parallel central kinetic field records obtained at approximately the same time. The upper left set (part A) was obtained from control point F. All other Westheimer function data were obtained fro test point G. The stippled or dotted areas on the fields represent the blind spot (Le unless otherwise de

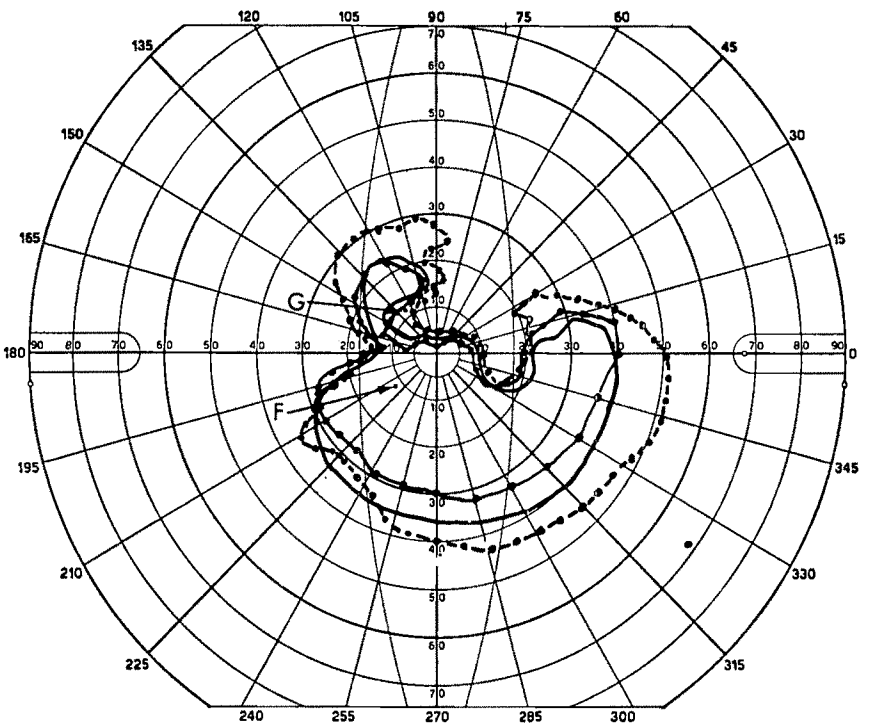


Fig. 14 (Enoch and Lawrence). Case 3, right eye. Kinetic I$_3$e visual field records, obtained during the early course of therapy for tobacco-alcohol amblyopia, show general kinetic field improvements that occurred parallel with other test parameters. Connected dots, Oct. 29, 1971; solid line, Nov. 15, 1971; dots and dashes, Dec. 8, 1971.

(Fig. 12, f). The kinetic field slowly deteriorated (Figs. 13, parts A, bottom, and B), The inhibition arm of the Westheimer function subsequently showed no improvement, including during the second course of treatment (Fig. 13, part B). The flashing static threshold at points F and G showed a fluctuating course over the years. The initial improvement in visual acuity in the fovea was largely maintained, with fluctuations occurring in the intervening period. Neither the symptom equivalent control medication nor diphenylhydantoin, administered for a 12-month period, substantially altered the measured parameters (Figs. 2, 9, 12, and 13, parts A and B).

The patient clearly improved with hyroxocobalamin therapy. Depending on the measured parameter, that improvement was sustained for a short or long period after cessation of the treatment. The second course of therapy (in terms of the measured parameters) did not seem to alter the continued slow downhill course of the visual response in his peripheral field.

Applanation tonometer determinations— We attempted to relate these measurements to Westheimer function and visual field changes. One patient (Case 2) maintained high pressures in her right eye. The changes in visual responses could not be anticipated on the basis of applanation tonometry, although continued pressures of 30 mm Hg would not improve long-term prognosis. Another patient (Case 1) exhibited pressure fluctuations in his left eye that correlated poorly with visual test changes.

There may have been a possible relation-

ship between the higher pressures recorded in the right eye of another patient (Case 3) in March and April 1972 (resulting in pilocarpine treatment) and subsequent central field and Westheimer function changes. In the Westheimer function experiment, Field I was set at 0.8 to 1.0 log unit above the flashing static threshold. Thus, even if the static threshold was altered, the Westheimer function should not have been meaningfully affected by alteration of pupil diameter. On the other hand, visual field determinations can be somewhat sensitive to changes in pupil size. The pupil of the last patient varied between 2 and 4 mm (in time). Since he was not reliable regarding the self-administration of medication, a registered nurse administered the hydroxocobalamin injections.

Discussion

No single parameter characterizes visual performance since several variables are at play at any given moment. Periodic exacerbations and remissions of disease processes tend to make attempted analyses difficult. Because of such fluctuations, it becomes desirable to follow the course of the individual patient.

We believe the Westheimer function and the flashing repeat static threshold tests are valuable additions to the visual field test armamentarium. We have shown how the Westheimer technique can be greatly speeded up in order to make it a more acceptable clinical test. From these data, significant alteration in response can be readily identified without complex statistical analysis. If one accepts the relatively conservative position of nonoverlap of data ranges as the criterion for meaningful change, then there can be little question of rejection of the null hypothesis in a more formal statistical analysis. Repeated testing resolves questions of reliability of the observer or of changes observed.

These tests can be used as part of a program to test sequentially the efficacy of a therapeutic regimen or to follow the course of an anomaly. The value of a data set is dependent on the proper selection of loci for test and control points. One makes use of one's knowledge of the course of the anomaly and picks those test loci that will probably provide valued data. The optimum sizes of background field to use at a given test point in studies of the Westheimer function were described.[2] If blur is corrected, there seems to be little variance in the dimensions of the function for most people, paying attention to spectacle magnification properties. The latter can often be assessed by plotting the normal blind spot and considering its field location and size.[12]

In this study we demonstrated the time course of change in the inhibition arm of the Westheimer function relative to kinetic visual field change (Case 1) in primary open-angle glaucoma. We clearly showed that the loss of the inhibition arm of the Westheimer function is reversible in primary open-angle glaucoma, at least to a certain stage in the disease (Case 2). We were able to differentiate the most probable cause of the loss of the inhibition arm of the Westheimer function in a complex of disease states, through analysis of several response parameters in conjunction with a therapeutic regimen in Case 3. That is, since anomalous response at point G in this patient comprised more than one response level (inner retinal layer and central to the optic nerve head), and since functional improvement occurred in all response parameters after therapy specifically for tobacco-alcohol amblyopia, we concluded that the most probable cause of the field deterioration at this point during the first course of therapy was the tobacco-alcohol amblyopia rather than the glaucoma. The Westheimer function at test point G in Case 3 showed inhibition loss and loss of sensitivity just before cessation of the hydroxocobalamin treatment, but the improvement in response to the flashing static perimetric test at the same point, foveal acuity, and the foveal Westheimer function were largely maintained. Thus, exacerbation of the dis-

ease process at visual field point G was probably limited to the inner retinal layer. Since the effects of tobacco-alcohol amblyopia were apparently not limited to the inner retinal layer initially, one could hypothesize that the exacerbation was caused by the primary open-angle glaucoma that clearly affects this region, or by the combined action of the glaucomatous disease process and the tobacco-alcohol amblyopia. The applanation tonometric determinations in March and April 1973 (Table 3) seem to lend weight to this argument. Neither diphenylhydantoin nor the control drug seemed to affect the course of the disease of this patient at this state of progression.

The data on one patient (Case 1) suggest another interesting finding (Fig. 5). There seemed to be recovery of the kinetic field, while at two separate points in the field the Westheimer function remained abnormal. The flashing static perimetric threshold also showed improvement on July 6, 1973 (Fig. 2). Repeat flashing static perimetric data were essentially normal on that date. This is the first time we recorded a clearly abnormal Westheimer function (loss of inhibition arm at two test points) while other response parameters at the same locus revealed relatively normal (or improved) function. Usually, we tested areas of abnormal function as a means of locating areas of abnormal Westheimer response. This finding suggests that this approach needs to be reconsidered.

Summary

We used a technique to simplify and speed up a perimetric test (Westheimer function). Through sequential testing, the technique was successfully used to evaluate pathologic findings and partially to evaluate treatment regimens in three subjects. One patient had an onset of kinetic field changes and Westheimer function alteration with primary open-angle glaucoma. Temporary remissions of alterations in the Westheimer function and kinetic visual field loss occurred in patients with glaucoma and tobacco-alcohol (complicated) amblyopia. Using these techniques it is possible to localize an anomaly in the outer retinal layer, the inner retinal layer, and central to the optic nerve head. We divided the inner and outer retinal layers on a vascular support basis.

Acknowledgment

We thank Kenneth Buerk, M.D., for patient selection; Allan Mandell, M.D., for assistance in preparing the summaries of patient histories; and Allan Kolker, M.D., for assistance in selecting the fields points tested in Case 1.

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MONOCULAR DIPLOPIA IN FLYING PERSONNEL

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Binocular diplopia is due to misalignment of the two visual axes, as in the presence of a paralytic extraocular muscle or failure of binocular fusion. Light from a single point in space is projected onto areas of the two retinas that do not correspond in their spatial orientation. Hence, two images are perceived. There is an obvious handicap and hazard if a pilot experiences this type of diplopia. Accordingly, U.S. Air Force physical standards disqualify personnel with diplopia as well as those with large heterophoric measurements.[1]

Monocular diplopia occurs when two images are represented on the retina of a single eye. It may be unilateral, involving only one eye, or bilateral, involving both eyes. Seeing three or more images is termed polyopia. Several different causes for this disorder have been reported. However, we have found no reports of monocular diplopia in flying personnel. We attempted to determine whether this type of diplopia is a hazard in flying or in other occupations requiring a comparable degree of visual performance. We document 15 persons with monocular diplopia or polyopia.

MATERIAL AND METHODS

We reviewed case records of U.S. Air Force flying personnel within the past five years. The primary criterion for selection in the study was that a patient spontaneously reported double or multiple images in his ordinary environment and that this phenomenon persisted with only one eye open. Routine ophthalmologic examination included distant and near visual acuity, phorias, stereoscopic vision, accommodation, color vision, tonometry, manifest and cycloplegic refraction, slit-lamp examination, and direct and indirect ophthalmoscopy. Many patients underwent keratometry, Goldmann perimetry, Amsler grid testing, pinhole vision testing, and various attempts to measure or manipulate the double or multiple imagery. Neurologic and psychiatric evaluations were normal in all patients. After reviewing available historical and examination data, we assigned a probable cause for the visual abnormality in each case.

RESULTS

Fifteen patients (Table 1) complained of monocular diplopia or polyopia. All were active pilots or navigators with at least four years' flying experience, ranging in age from 26 to 49 years. Of these 15 patients, nine had unilateral involvement and six had bilateral involvement totalling 21 affected eyes.

Best visual acuity had been recorded at the initial examination for the complaint, whether uncorrected or corrected by spectacles or contact lenses. In three cases reported as resolved, because records were unavailable from the time of occurrence of the symptom, acuity at the time of examination was reported. Sixteen of the 21 eyes had acuities of 20/15 or better, and in eight of these 16, diplopia was demonstrated with visual acuities of 20/15 or better.

In all instances the double image was only a faint shadow or ghost image seen at contrasting borders or around bright objects and did not present any confusion to the observer as to the identity of the real image. In four patients, we measured the separation between the images ranging from 5 to 10 minutes of arc.

Pinhole viewing eliminated or markedly reduced the prominence of the secondary image in the 19 eyes using this device. Other means of reducing the image included cor-

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TABLE 1

DATA ON PATIENTS WITH MONOCULAR DIPLOPIA OR POLYOPIA*

Case No., Age	Best Visual Acuity	Characteristics And Location of Abnormal Image	Improvement of Abnormal Image		Other Significant Findings	Cause of Abnormal Image	Remarks
			Pinhole	Other			
1, 32	RE 20/15, u LE† 20/20, s	NR	NR	Contact lens Eyelid	Irregular corneal astigmatism	Transient corneal astigmatism, unknown cause	Resolved over few months
2, 37	RE 20/15, s LE† 20/15, s+c	Down, multiple when dilated	NR	Contact lens Spectacle lens	Corneal lens opacity	Possibly lenticular astigmatism	
3, 42	RE 20/15, u LE† 20/15, u	NR	+		Posterior lens irregularity	Possibly lenticular irregularity	
4, 38	RE† 20/15, u LE† 20/15, u	Up, 8 in	+	−1.00 lens	Mild nuclear sclerosis	Lenticular irregularity	
5, 43	RE† 20/15, c LE† 20/15, c	Up	+	Contact lens	Keratometry distorted	Irregular corneal astigmatism	13-yr wear of poorly fitting contact lens
6, 26	RE† 20/10, u LE† 20/10, u	Up, 10 in	+	Contact lens	LE blepharoptosis, band across red reflex	Corneal irregularity possibly due to blepharoptosis	
7, 40	RE 20/15, s LE† 20/20, s	Up, left	+		Corneal astigmatism LE>RE	Possibly corneal astigmatism	
8, 46	RE† 20/40, s LE† 20/25, s	Multiple, most prominent at night	+		Marked nuclear sclerosis; bull's-eye red reflex	Early nuclear cataracts	
9, 43	RE† 20/15, u LE 20/15, u	Left, 7 in	+	−1.00 lens	Irregular red reflex	Lenticular irregularity	
10, 34	RE† 20/15, s LE 20/15, s	Up, left 5 in	+	Refraction	Corneal astigmatism RE>LE; chalazion, upper right eyelid	Corneal distortion due to chalazion	History paralleled development of chalazion; resolved after treatment
11, 35	RE 20/12, u LE† 20/25+, s	NR	+		Iridodialysis, posterior subcapsular cataract	Extrapupillary aperture or cataract	Only on viewing bright object at night
12, 31	RE† 20/15, s LE† 20/15, s	RE worse	+	Refraction	Astigmatism	Uncorrected astigmatism	LE resolved; RE minimal without glasses
13, 36	RE† 20/15, s LE† 20/15, s	Up	+	Eyelid	Astigmatism; macular pigment dispersion, probably traumatic	Possibly uncorrected astigmatism	Resolved
14, 49	RE† 20/15, s LE† 20/15, s	Lateral	+		Astigmatism, hyperopia	Possibly weakness of accommodation	Resolved
15, 45	RE† 20/15, s LE 20/15, s	Up	+	Eyelid	Traumatic iridodialysis	Extrapupillary aperture	Only on viewing bright object at night with eye wide open

* NR indicates not recorded; u, uncorrected; s, spectacle lens; c, contact lens.
† Affected eye.

tact lenses, careful refraction for spectacles, and minus lenses to stimulate accommodation. In one instance, we prescribed a correction solely to eliminate the ghost image. However, four other patients experienced reduction of the ghost image in the course of correction to best visual acuity by spectacles or contact lenses. The remaining patients, whose visual aberrations had not improved, accepted it as a minor nuisance.

In five patients the double image resolved or improved during or before the period of ophthalmologic observation. One patient (Case 1) had a transient episode of irregular corneal astigmatism of unknown etiology. Another (Case 10) reported improvement after treatment of a chalazion. Three others noted their visual aberration while in captivity as prisoners-of-war, and reported marked improvement after repatriation. A contributing factor in such cases may have been a tendency by these men to pay close attention to minute details of their surroundings and perceptions, and thus notice phenomena that normally may have been overlooked.

While it was impossible in many cases to be certain of an etiology, we assigned a likely cause based on available information from history and physical examination. All cases appeared due to intraocular optical factors, with five cases probably lenticular in origin, and five probably corneal. Three others appeared due to refractive or accommodative factors, and two due to an abnormal aperture in the iris.

CASE REPORTS

Case 4—This 38-year-old man experienced vertical doubling of distant objects with either eye, especially when viewing objects against a contrasting background. Refraction provided no improvement. Initial examination revealed only mild granularity of the macular retinal pigment epithelium. With a tentative diagnosis of macular degeneration, the patient was referred here.

Uncorrected visual acuity was 20/15 in each eye, with emmetropia on manifest and cycloplegic refraction. Slit-lamp and red reflex observation of the lens revealed mild nuclear sclerosis. The macular pigment epithelium was granular, but evaluation by slit lamp, perimetry studies, color vision, and fluorescein angiography failed to support a diagnosis of macular degeneration.

The visual abnormality consisted of a secondary image displaced upward about 8 minutes of arc. It was readily visible under a variety of conditions of illumination. Although not normally noticed at near, it appeared when accommodation was relaxed by plus lenses. The secondary image was completely eliminated by pinhole viewing, and nearly eliminated by —1.00 lenses. The change with accommodation suggested that a lens abnormality such as nuclear sclerosis was responsible.

Although acuity and other functions were completely acceptable for USAF flying standards, the patient elected to wear —1.00 lenses as a distance correction.

Case 10—This 34-year-old man noted slight blurring with the right eye, which he gradually perceived as a double or ghost image, displaced slightly upward and to the left of the primary image. Approximately one month earlier a nodule had appeared in the right upper eyelid, and it was diagnosed as a chalazion. After reporting the double vision to his flight surgeon, the patient was grounded and referred for evaluation.

Uncorrected visual acuity was R.E.: 20/20, and L.E.: 20/25, correctable to 20/15 in each eye (R.E.: plano —0.25 cyl, axis 120°, but variable on repeated testing; L.E.: —0.50). A 3- to 4-mm nontender nodule was palpable in the center of the right upper eyelid. Keratometry revealed greater corneal astigmatism in the right eye, with an oblique axis. The remainder of the examination was normal.

The double image was about 5 minutes up and to the left of the primary image. It was completely eliminated by pinhole viewing, and nearly eliminated by various refractive manipulations. By careful positioning of the pinhole, the patient viewed either image alone. Incision and curettage of the chalazion were performed; after resolution of postoperative edema, the double image was no longer perceived. Five months later, neither the chalazion nor the diplopia recurred.

DISCUSSION

It is often assumed that monocular diplopia has a psychiatric rather than ophthalmologic origin. This study supports the belief that monocular diplopia is rarely caused by psychiatric conditions.

TABLE 2

CLASSIFICATION OF MONOCULAR DIPLOPIA

Factors
Extraocular optical
Organic
Physiologic (normally asymptomatic)
Pathologic (symptomatic)
Optical aberrations
Retinal lesions
Strabismus
Cerebral lesions
Psychogenic

The types and causes of monocular diplopia are classified in Table 2. It is easy to demonstrate that extraocular devices, such as prisms or spectacles, can be manipulated to produce a double image in one eye. However, our concern was the possible presence of organic factors altering visual perception at the level of either the eye or the brain.

"Physiologic" monocular diplopia, demonstrated in many normal subjects by special testing situations and devices,[2] is probably due to slight imperfections in the eye, such as failure of the optical axes of the cornea and lens to be perfectly aligned.[3,4] These aberrations are usually asymptomatic, and the visual effects they produce are ignored by all but the most astute observers. Another physiologic variety of monocular diplopia is the double vision that occurs when a line is brought closer to the eye than the near point of accommodation.

"Pathologic" monocular diplopia is symptomatic under ordinary viewing conditions and is attributed to an identifiable abnormality of the visual system. Optical aberrations in the refracting elements or transparent media of the eye are common, understandable causes. Examples of such abnormalities are cataracts, extrapupillary apertures (iridectomy, iridodialysis), subluxated lens, and irregular astigmatism. The effect is explained by variations in prismatic power in different areas of the pupillary aperture (Fig. 1). Limiting the aperture,

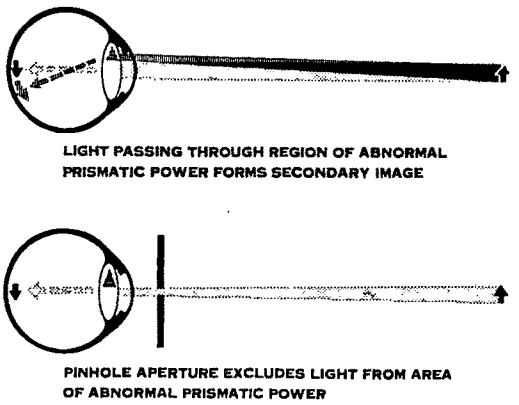


Fig. 1 (Stampfer and Tredici). Optical variations within the eye causing monocular diplopia (top). Elimination of secondary image by pinhole aperture (bottom).

as in pinhole viewing or miosis, restricts light to a more uniform area and eliminates secondary imagery. Several cases due to such optical causes have been reported, and in most instances the lens has been thought to be the site of optical abnormality.[2-5]

Other causes are less common. Retinal abnormalities of various types have been cited,[6-8] but case reports are difficult to find. Strabismus surgery can result in a transient period of monocular diplopia or binocular triplopia as the previously deviating eye realigns its visual direction and, for a time, perceives two directions as straight ahead.[9] Cerebral lesions (such as injuries, tumors, and vascular accidents) have caused some forms of multiple imagery.[10] Finally, psychological factors were often blamed for patients' complaints of monocular double vision, and may have been responsible in a few instances.

The distinction between physiologic and pathologic causes is not always obvious, and may be particularly ambiguous in our group of patients. Aircrew members generally have superior visual acuity and may be unusually attentive to slight changes in vision that many persons would fail to appreciate.

Monocular diplopia can be troublesome to any patient but may be particularly important in aviation or in any occupation requiring good visual performance and strict adherence to visual standards. It may indicate the presence of a disease process, be a significant visual detriment, or act as a source of annoyance that may impair efficient and safe functioning. Only one of four patients had a serious and apparently progressive condition: bilateral nuclear cataracts with decreased visual acuity. All other patients maintained or recovered excellent visual acuity and passing performance on all visual function tests.

If, as in our cases, secondary images appear only as faint overlapping ghost images along contrasting and well-defined borders, the likelihood of confusion is remote. With normal acuity and binocular fusion, depth perception and stereoscopic vision are undisturbed and spatial localization and orientation are not as complicated as in binocular diplopia.

While several patients were initially annoyed and worried about the secondary images, they were reassured by an explanation and by our findings that no pathology seemed responsible.

In general, in the presence of normal acuity and other visual functions, monocular diplopia due to optical aberrations is not usually a detriment to safe and accurate performance in flying or in other activities requiring a comparable degree of visual proficiency. Of course, each case should be evaluated fully and followed periodically to detect any subsequent deterioration of visual function.

If spectacles improve the visual aberration and the patient is willing, they should be provided. Elimination of secondary images by contact lens has been reported,[11] and occurred in several of our cases. However, contact lenses are used in U.S. Air Force flying personnel only in selected cases when spectacles do not achieve required visual acuity. Miotics have produced a "pharmaco ogic p nhole,"[12] but military aviators do not use them because of possible refractive changes and diminution of night and peripheral vision.

In evaluating a patient with this complaint, the history of onset and diplopia characteristics should first be determined and visual acuity measured. To determine whether the diplopia is monocular, the examiner simply covers each eye in turn to make certain that it does persist on monocular viewing. The simplest and most useful test is to have the patient look through a pinhole of 1 to 2 mm in diameter. Elimination of secondary images by this means is good evidence for an optical cause. Examination of the red fundus reflex with the retinoscope or direct ophthalmoscope may reveal areas of varying optical density (Fig. 2).

This simple battery of tests usually elucidates the cause of monocular diplopia. However, if it is due to causes other than ocular optical aberrations, more extensive investigations may be required.

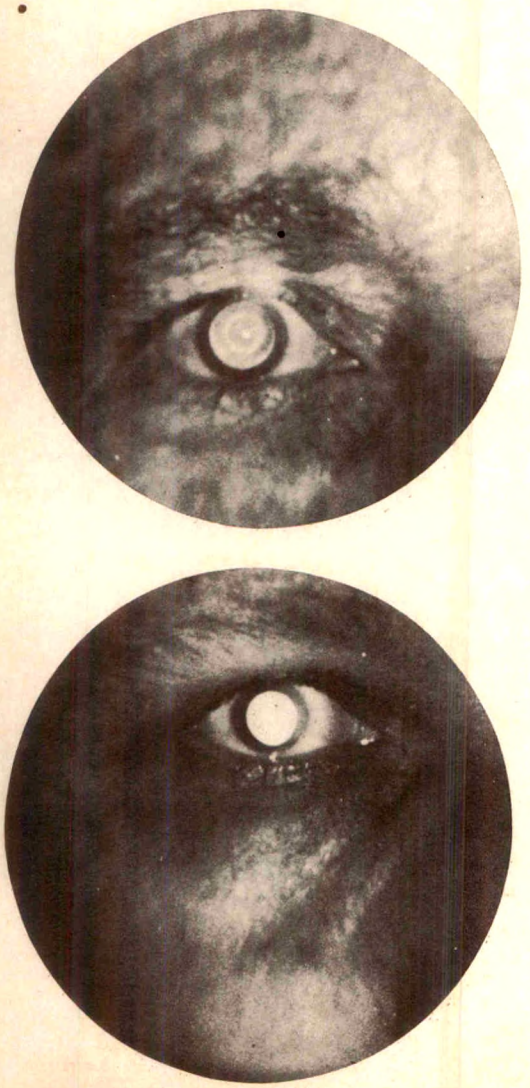


Fig. 2 (Stampfer and Tredici). Top, Abnormal red reflex forming bull's-eye pattern in monocular polyopia due to advanced nuclear sclerosis. Bottom, Normal red reflex photographed under similar conditions.

Summary

Fifteen cases of monocular diplopia or polyopia in U.S. Air Force flying personnel appeared due to optical aberrations or physiologic variations within the refracting elements of the eye. In most cases, this symptom was compatible with excellent visual acuity and was not regarded as a detriment to safe and accurate visual performance.

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NOTES, CASES, INSTRUMENTS

VITRECTOMY AND INTRAOCULAR GENTAMICIN MANAGEMENT OF *HERELLEA* ENDOPHTHALMITIS AFTER INCOMPLETE PHACOEMULSIFICATION

GHOLAM A. PEYMAN, M.D., DAVID W. VASTINE, M.D., AND JAMES G. DIAMOND, M.D.

Chicago, Illinois

Although the incidence of endophthalmitis after routine cataract extraction has been well documented,[1] to our knowledge it has not been reported after phacoemulsification. We treated *Herellea* endophthalmitis after phacoemulsification with vitrectomy and intravitreal antibiotic infusion.

CASE REPORT

A 63-year-old white woman had progressive decrease in visual acuity in her right eye. She had had previous cataract surgery in the left eye in 1972. Results of her general physical examination and laboratory studies were normal. Her best corrected visual acuity was R.E.: 20/200 and L.E.: 20/25 with +8.25 sph +2.75 cyl × 25° correction. Ophthalmic examination showed surgical aphakia of her left eye and an immature cataract in the right eye.

On May 30, 1974, the patient underwent a planned extracapsular cataract extraction in the right eye with the Kelman phacoemulsification apparatus.[2] The procedure was complicated by rupture of the posterior capsule and vitreous loss with part of the nucleus and lens remnants left intraocularly at the end of the procedure. The patient received 25 mg of cephaloridine subconjunctivally and 500 mg of oxacillin orally at the end of the procedure and every six hours thereafter. On the first postoperative day she had a moderate postoperative reaction with 2+ flare and cells, poor red reflex, and low intraocular pressure. Systemic prednisone, 60 mg daily, was administered together with topical hydrocortisone sulfate (Neo-Cortef 1.5%) every two hours. Forty-eight hours after surgery, the patient developed moderate discomfort without tenderness or chemosis of the upper eyelid. There was a marked perilimbal reaction, a 3-mm hypopyon, vitreous debris, poor to absent red reflex with intraocular pressure of 20 mm Hg. From the signs and symptoms it was not clear whether the intraocular inflammation was from lens-induced uveitis or bacterial endophthalmitis, or both. A radical anterior vitrectomy was performed with the vitrophage through a pars plana incision.[3] Most of the iris, the white exudate in the vitreous body, and lens remnants were removed. Poor visibility prevented complete removal of the opaque vitreous fluid. The infusion fluid used throughout the procedure contained 8 μg/ml of gentamicin sulfate. At the end of the procedure, 400 μg of dexamethasone was injected into the anterior chamber. Postoperatively, the patient was maintained on orally administered prednisone, 60 mg daily, and oxacillin, 500 mg administered orally every six hours. Treatment with 60 mg of intramuscularly administered gentamicin every eight hours and ampicillin, 1 g administered intravenously every six hours, was instituted. The systemic oxacillin was discontinued. Forty-six hours after surgery, visual acuity was light perception with projection, the corneal haze had cleared, and the red reflex was improved. There were 2+ cells and flare without hypopyon. Cultures revealed a gram-negative rod and further studies identified the organism as *Herellea* resistant to ampicillin and oxacillin. The intravenously administered ampicillin was discontinued.

After one week of treatment, the patient was discharged on a regimen of 60 mg of prednisone daily with 500 mg of tetracycline every six hours. The corneal edema had cleared considerably, the red reflex was improved, with continued light perception with good projection. The anterior chamber contained 1+ cells and flare.

On routine follow-up examination one month after the first procedure, a large remnant of the lens nucleus was noted in the anterior chamber. There was an increased anterior chamber reaction despite 40 mg of prednisone daily and topical Neo-Cortef 1.5% four times a day. Visual acuity had improved to hand motions. Indirect ophthalmoscopy showed a mild vitreous reaction; the retina was attached. The patient had a second vitrectomy with removal of the lens material that could not be adequately visualized during the first operation. The postoperative course was uneventful except for marked striate keratopathy. The patient was discharged on a regimen of prednisone, 60 mg orally each day, and topical atropine.

Six months after the onset of the endophthalmitis, the patient still had mild striate keratopathy. Her visual acuity was now 20/80 with a soft contact lens and overrefraction of +10.25 sph +25 cyl × 20°. The intraocular pressure was 18 mm Hg. The retina was attached and appeared normal. The anterior chamber was quiet without medication.

From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago. This study was supported in part by grant 1107-02 from the Public Health Service, and by the Illinois Lions Club.

Reprint requests to Gholam A. Peyman, M.D., University of Illinois Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612.

Discussion

The occurrence of *Herellea* endophthalmitis in a complicated phacoemulsification procedure is, to our knowledge, without reported precedent. More intense ocular inflammation can be expected if lens nucleus is left in the anterior chamber and the posterior capsule is ruptured with vitreous loss. The surgical complications and rapid onset of intense ocular inflammation would have made separation of lens-induced uveitis from endophthalmitis impossible were it not for culture-positive identification of an infecting organism. The presence of lens-induced uveitis with proteinaceous anterior chamber fluid may act as an excellent culture medium for organisms accidentally introduced during complicated cataract or phacoemulsification procedures.

This patient may have carried *Herellea* in the conjunctiva without overt evidence of conjunctivitis. After introduction into the anterior chamber during the operative procedure, it grew readily in a rich protein medium resulting from the lens remnants and exudative reaction of the eye after incomplete phacoemulsification.

This case probably represents the presence of both lens-induced and bacterial endophthalmitis.

Vitrectomy to remove residual lens material, performed in conjunction with the intravitreal injection or infusion of the appropriate antibiotics,[4,5] results in the rapid destruction of the remaining infecting organisms, and intraoperative treatment with dexamethasone and postoperative systemic corticosteroids suppresses intraocular inflammation.

Summary

A patient with *Herellea* endophthalmitis after incomplete phacoemulsification was treated with vitrectomy and intravitreal infusion of 8 μg/ml of gentamicin and 400 μg of dexamethasone. The vitrectomies were done through a pars plana incision with the vitrophage. Additionally, appropriate systemic antibiotics and prednisone were given.

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TRANSILLUMINATION OF THE ANGULAR AND FRONTAL VEINS

Samuel W. Cohen, M.D.,
William Banko, and
Noel Nusbacher, M.D.
Brooklyn, New York

A powerful "cold" light using a fiber optics bundle was used to transilluminate the angular and frontal veins.

The light source* (500 W) for the flexible fiber optics bundle provides a high intensity illumination with an initial 14,000 lumens. The bulb for this source is a tungsten-halogen lamp that emits an approximate color temperature of 3,200°K. This 500-W light source is approximately 3½ times the

Reprint requests to Samuel W. Cohen, M.D., 522 Ocean Ave., Brooklyn, NY 11226.

* The 500-W light source is available from Surgical Design Corporation, 24-05 Jackson Ave., Long Island City, NY 11101.

From the Departments of Ophthalmology and Radiology, Jewish Hospital and Medical Center of Brooklyn, Brooklyn, New York.

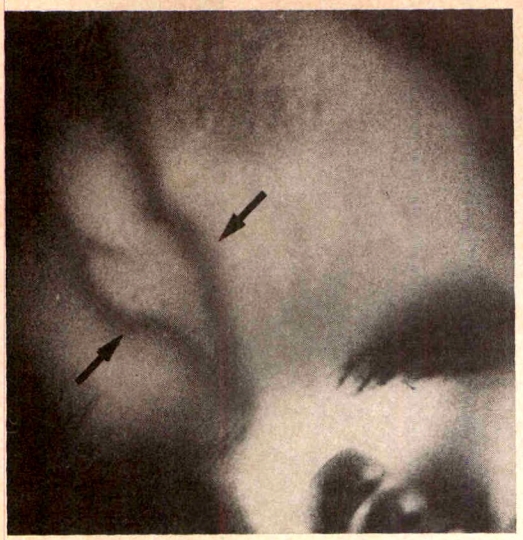


Fig. 1 (Cohen, Banko, and Nusbacher). Frontal veins, as indicated by arrows, as seen by transillumination.

power now available from standard commercial light sources.

The angular vein is transilluminated as follows: The fiber optic cable is introduced into the external nares of each side. This causes a transilluminating glow of the bridge of the nose and upper cheek and nasal canthus of the corresponding side. The angular vein is located immediately and stands out in excellent contrast from the surrounding tissues. This is helpful in doing angular vein orbital venography by the percutaneous technique as well as assisting the surgeon during the lacrimal sac procedures to avoid cutting the vein. It is possible to compress the angular vein by graduated pressure over the vein, as from an ophthalmodynamometer, and visualizing the interruption of its blood flow. This may be useful in estimating venous pressure within the superior ophthalmic vein or sinus cavernosus. Further studies of this are necessary, however.

The frontal veins are also well transilluminated if the fiber optics bundle is held firm against the superior orbital ridge near the medial border (Fig. 1). This has proved

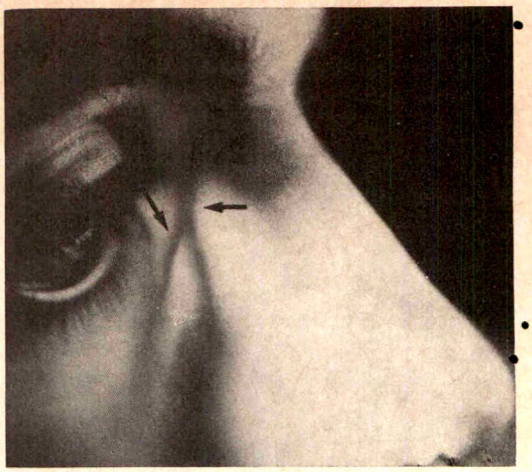


Fig. 2 (Cohen, Banko, and Nusbacher). Anterior facial vein anastomosing with angular vein as seen by transillumination.

extremely useful for introducing a needle into the frontal vein in performing the frontal vein techniques of orbital venography and thus avoiding the Trendelenburg position and compressing of jugular veins as has been conventionally recommended.

Using the powerful cold light, we have been able to identify the angular and frontal veins in all of our patients, whether light skinned or dark skinned. In some instances, we were also able to identify the branch of the anterior facial vein anastomosing with the angular vein (Fig. 2). But no clinical application has as yet been done of this.

Summary

A 500-W fiber optics cold light used to transilluminate the angular and frontal veins allowed quick, accurate delineation of the veins for percutaneous orbital venography. It also allowed the surgeon to avoid cutting the angular vein when operating on the lacrimal sac.

VITREOUS SCISSORS AND FORCEPS

GHOLAM A. PEYMAN, M.D., AND FELIPE U. HUAMONTE, M.D.
Chicago, Illinois

Occasionally during vitrectomy the retropupillary membranes are unpliable at the vitrophage opening.[1] Cutting these membranes into small pieces renders them flexible enough to be removed with the vitrophage. The difference between our scissors and others is that the blades are angled to approach the bands from different directions (Figure). The scissors are equipped with a fine infusion tube permitting maintenance of intraocular pressure during the operations.

Forceps were developed for removal of nonmagnetic foreign bodies. The wide jaws of the forceps are bent against the shaft (Figure), thus permitting good visualization. In addition, they are large enough to grasp easily large intraocular foreign bodies, thus overcoming a problem with existing vitreous forceps.

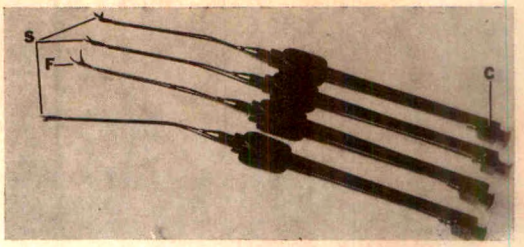


Figure (Peyman and Huamonte). Vitreous scissors (S) with angled blades and forceps (F); C indicates inferior cannula.

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SUMMARY

Vitreous scissors with bent blades and forceps of larger than usual dimension were developed for removal of inflexible membranes and intraocular foreign bodies.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

THIRD INTERNATIONAL ORTHOPTIC CONGRESS

Organized by the American Association of Certified Orthoptists and under the auspices of the International Orthoptic Association, the Third International Orthoptic Congress was held July 1-3, 1975. Boston, bathed in sunshine and at the eve of the bicentennial celebration, served as a charming hostess for this memorable event. Orthoptists and ophthalmologists from more than 20 nations participated in what turned out to be a truly outstanding program. The opening ceremony on the eve of the Congress included welcoming remarks by representatives from various orthoptic organizations and an address by Edmond Cooper who read a speech prepared by Hermann Burian before his death. Dr. Burian was to be president of honor of this Congress. After the opening ceremony, over wine and cheese, an informal get-together provided the appropriate atmosphere for greeting old friends and making new ones, an activity that makes international meetings such a pleasure to attend.

For the next three days, there followed a densely packed scientific program, covering nearly all aspects of recent advances in the diagnosis and management of strabismus. Related subjects were grouped into 13 sessions, each followed by extensive round table discussions that were skillfully moderated by strabismologists of international repute. Nearly all papers were of good quality, well presented and illustrated.

I was especially impressed by the scientific quality and excellence of presentation of those papers given by orthoptists. At a time when there is much concern among American orthoptists about becoming absorbed and perhaps replaced by other allied health personnel in ophthalmology, the contribution made by orthoptists at this Congress demonstrated clearly that orthoptics must continue independently as an integral aspect of ophthalmology.

After the long scientific sessions, the social functions in the evenings were especially enjoyable. There was a dinner party at the New England Aquarium, where the beauty of the ladies milling in semi-darkness about a gigantic tank filled with sharks and other vicious creatures provided a rather unique contrast. The delegates also enjoyed a champagne reception at the Isabella Stewart Gardner Museum by invitation of the American and Canadian Orthoptic Associatons.

The Congress was summarized and closed by Mr. Keith Lyle, of Great Britain, after which the new chairman of the International Orthoptic Association, Miss Attie van Paassen, The Netherlands, was installed by the outgoing chairman, Miss Barbara N. Lee, of Great Britain. The proceedings of this Congress will be published by Symposia Specialists Medical Books.

The Fourth International Orthoptic Congress will convene in 1979 in Berne, Switzerland.

GUNTER K. VON NOORDEN

The Third International Orthoptic Congress was held in Boston, Massachusets, July 1-3, 1975. Barbara Lee, president of the International Orthoptic Association, and Evelyn Tomlinson, president of the American Association of Certified Orthoptists, presided jointly at the opening ceremony. Edmond L. Cooper gave the opening address which had been written by Hermann Burian for this occasion. The warm, personal words of welcome stressed the importance of international meetings in order that we might learn from our differences and the meeting opened with the champagne toast as Dr. Burian had wished.

The scientific sessions were interesting and provocative and the ensuing discussions especially stimulating. David H. Hubel pre-

sented a paper describing the results of his work in experimental amblyopia. He showed two principal factors that caused disruption of developmental function in the visual cortex: (1) light and form deprivation at the time of high susceptibility, and (2) abnormal binocular interaction. Gunter K. von Noorden discussed these current concepts of amblyopia. The necessity of treating amblyopia early was reinforced, but it was suggested that we refrain from using all day occlusion in a child under one year of age.

Dorothy Hedden was chairman and David Cogan was moderator for the session dealing with nystagmus. L. F. Dell'Osso presented a paper dealing with the necessity for quantitative measurements, including velocity tracings of eye movements in congenital nystagmus. After determining the null angle, he uses prisms or surgery to put the patient's eyes at this angle. Dr. Dell'Osso contends that when the patient uses a compensatory head posture to be at this null position, he has put forth effort which builds up the nystagmus and sacrifices visual acuity. H. Muhlendyck delivered a most controversial paper dealing with the Cuppers "Faden" operation in the treatment of convergent strabismus associated with latent nystagmus. With this procedure he changes the arc of contact of the medial rectus muscle by removing it from its insertion, placing two sutures 12 to 16 mm behind the insertion, anchoring it to the globe, and then reattaching the muscle at its original insertion.

Barbara Lee was chairman for the session dealing with prisms. Wm. Rubin, S. Veronneau-Troutman, P. V. Berard, Aimee Beressi, Lynn Stockbridge, and Madame Françoise Zamfirescu provided practical papers at this session. Prisms were reported as a safe and versatile tool in the treatment of primary exotropia, paralytic deviations, amblyopia with eccentric fixation, and as a preoperative diagnostic tool to determine the importance of a vertical component associated with esotropia.

Edward A. Dunlap was chairman and R. B. Hartcourt was moderator for the session dealing with dysthyroid eye disease, which has an unpredictable course with changes seen over a period of as long as ten years.

The treatment of strabismus in children with cerebral palsy was discussed by Judith H. Seaber. With the exception of the known variables, traditional therapy gave results comparable to those found in children without cerebral palsy. Thomas D. France reported that strabismus is the most common ocular complication of hydrocephalus, with a high incidence of an "A" pattern. He reported good results achieved with patching and surgery. Surgery was usually performed after one year. In the treatment of developmentally handicapped children, Diana Thornhill reported that functional results were not to be hoped for in many cases.

Valerie Kelly delivered a most interesting paper on ocular motor defects associated with herpes zoster ophthalmicus. The overall incidence of defects was far greater than originally reported, and some patients have demonstrated contralateral involvement.

Donelson Manley reported on superior oblique palsy and his choice of surgical procedure. Dr. Manley suggested that a graded recession of the yoke or a recession of the antagonist, after a wait of nine to 12 months, gave most satisfactory results.

R. S. Jampel and R. A. Crone reported differing opinions on the question of cyclofusion. Dr. Jampel stated that recent experimental work has shown cyclofusion responses are mediated by central mechanisms without any compensatory eye movements and therefore there is no motor component to cyclodeviations. Dr. Crone held with the traditional view.

The final day's scientific sessions dealt with a montage of topics. Among them was Leonard Apt's paper on the derivation of a linear equation and curve as a method of relating eye position under anesthesia to outcome of surgery. Dr. Apt showed that pa-

tients with a normal amount of divergence under anesthesia had a higher rate of successful results postoperatively. G. H. Gobin reported on his results with four muscle surgery in "V" esotropia. He displaces the insertions of both inferior oblique muscles toward the equator, thus enlarging the angle between the muscle and the vertical axis. In this way he selectively reduces vertical in favor of torsional action. He believes the real barrier to fusion is the torsional dimension. To this procedure is added a bilateral medial rectus recession of at least 5 mm. Phillip Knapp reported on 50 cases of bimedial recessions with bare scleral closure, achieving an average correction of over 40 prism diopters. W. J. Gillie's paper supported a single muscle procedure as the best choice as a reoperative procedure in convergent strabismus. Marshall M. Parks delivered a paper supporting extirpation of the inferior oblique muscle in cases of recurrent overaction. He advised this only after a careful search has been made to insure that no portion of the muscle remains attached. His choice for initial surgery is an inferior oblique recession. John S. Hermann's paper dealt with the use of anchoring sutures in the overcorrected position for a period of two weeks in strabismus patients who develop excessive and adhesive fibrosis and cannot be managed in any other manner.

The final session of the Congress concerned exotropia. Edward L. Rabb suggested that the best results were obtained when exotropic patients were overcorrected surgically, whether fusion was present or not. R. Mervyn Brown delivered a paper on consecutive exotropia. In his study early consecutive exotropia was most often caused by a medial rectus limitation, while later divergence was found attributable to amblyopia and poor binocular function. Orthoptics was generally believed to be necessary in the treatment of exotropia, although whether treatment is more beneficial pre- or postoperatively was debated.

T. K. Lyle closed the scientific sessions with words of praise for a job well done to Joyce Mein, chairman of the Scientific Committee. Professor Lyle noted that the Congress had brought both researchers and clinicians together to share in the medical care of patients.

JANE DUNN LAVOIE

CHICAGO OPHTHALMOLOGICAL SOCIETY CLINICAL CONFERENCE

The Chicago Ophthalmological Society held its annual Clinical Conference at the Drake Hotel, Chicago, on May 23 and 24, under the co-chairmanship of Thomas Chalkley and Joel A. Kaplan. J. Graham Dobbie's address of welcome was followed by a discussion of fungal keratitis by Dan B. Jones. Jorge N. Buxton spoke on glaucoma after keratoplasty.

In his paper on complications of intraocular lenses, Norman Sanders summarized the Bascom Palmer Eye Institute's five-year study of the Copeland intraocular lens. Although no comparable study of cataract cases without intraocular lenses was available, it appeared that there was a greater overall complication rate when an intraocular lens was inserted. Because of the increased risk, Dr. Sanders emphasized the need for careful consideration of each patient in whom an intraocular lens is contemplated.

Deborah Pavan-Langston spoke on the diagnosis and management of herpes simplex. The multifaceted nature of ocular herpes simplex has become more clearly defined in recent years as a disease characterized by both infectious and immune components. Therapy of infectious epithelial dendritic-geographic disease is generally gentle debridement of the ulcer followed by antimetabolite chemotherapy with IDU or adenine arabinoside. Trophic (metaherpetic) ulceration may occur after infection and is due to sterile damage of the basement membrane, which makes it difficult for the epithelium to heal across the damaged ulcer base. Therapy generally involves patching,

soft contact lenses, and lubricating eyedrops and ointment.

Stromal disease may be viral interstitial keratitis, which is slowly responsive to antiviral therapy, or an immune disciform reaction, which may necessitate corticosteroid therapy with prophylactive antiviral and antibiotic cover.

Herpetic iritis may occur alone or with any form of corneal disease. Therapy is corticosteroid oriented for lack of more effective and penetrating antiviral drugs. Antimetabolite-induced medicamentosa may mimic almost any form of herpetic disease and should be considered in any differential diagnosis of a patient declining under therapy.

Lorenz E. Zimmerman gave the 31st Annual Gifford Memorial Lecture, "Orbital tumors of childhood."

In his study of lamellar keratoplasty, Norman Sanders found that few partial thickness grafts are being performed. Thus, the average resident and clinician sees and does a small number of these cases. Because of the lack of familiarity with this procedure, the tendency is to do a penetrating keratoplasty in cases in which a lamellar corneal transplantation would be preferable.

Deborah Pavan-Langston discussed keratoplasty in ocular herpes. The outlook for this type of therapy in herpetic keratitis has improved significantly over the past decade. While only two or three grafts in vascularized eyes, regrafts, and eyes with active disease are clear after two years, in quiet eyes with no significant vascularization, the success rate exceeds 80%. The significant factors in the improved results, in both favorable and unfavorable cases, are the improved surgical techniques, especially the operating microscope and 10-0 nylon sutures, and the increased understanding of the pathophysiology of corneal grafting resulting in more sophisticated postoperative care. In our experience, the routine use of high levels of corticosteroids in the immediate postoperative period, followed by a rapid tapering of these medications has been particularly successful.

Dan B. Jones discussed the management of nonmicrobial keratitis, and Jorge N. Buxton spoke on the preoperative and postoperative considerations in keratoplasty. William F. Hughes was moderator for the panel discussion on new material in corneal therapeutics.

Arnall Patz reported that further follow-up of the patients in the original study on diabetic macular edema and in the study of new patients emphasized the limitations of long-term control of this complication of diabetic retinopathy. The data indicated that photocoagulation for macular edema, even when successful, was frequently only a temporizing measure. Temporary stabilization occurred in favorable cases. Despite repeated treatments, however, further deterioration was observed in several patients during a longer period of follow-up. These findings did not refute the data of the original controlled study for treatment did slow the rate of deterioration.

D. Jackson Coleman discussed ultrasonography in the preoperative evaluation of vitrectomy. He found that opacifications of the ocular media resulting from vitreous hemorrhage prevented adequate visual evaluation of the interior of the globe. However, ultrasonography can portray both the extent of the hemorrhagic changes as well as such ocular pathologic alterations as retinal detachment, ocular tumor, and intraocular foreign bodies that may be obscured by hemorrhage. In the preoperative evaluation of patients for vitrectomy, a differentiation may be reliably made between diffuse and organized hemorrhage, vitreous membranes and retinal detachment, based upon topographic configuration and amplitude patterns. The graphic portrayal of the hemorrhage, as well as of co-existing pathologic changes resulting from trauma or diabetes, allows the vitreous surgeon to proceed in a more knowledgable manner.

In discussing unilateral exophthalmos,

William Cooper reported that the evaluation of unilateral exophthalmos requires, initially, that one be able to recognize the condition. The findings on physical examination in conjunction with plane films, tomograms, EMI scan, and orbital ultrasonography allow one to arrive at a presumptive diagnosis and accurate localization. It is necessary to rule out thyroid disease in these patients and to resort to the T3 suppression test of Werner in most cases.

Speaking on peripheral uveitis, Robert J. Brockhurst remarked that the pathogenesis of this disease is not well understood and that additional complications of the condition are now being recognized. The disorder may well be the result of a primary diffuse periphlebitis of the retinal veins. Fluorescein angiography supports this thesis by revealing multifocal areas of periphlebitis with leakage of serous fluid into the retina and vitreous. Observations also suggest that hemorrhage into the retina and vitreous may result from secondary neovascularization in the massive exudates, as well as by traction on retinal vessels by abnormal vitreous membranes. Also secondary retinoschisis may complicate this disorder, mimicking inferior retinal detachment.

Dr. Cooper's second presentation, ocular and orbital tumors, was limited to uveal melanomas and retinoblastoma. In the management of most iris melanomas, the case should be observed until the angle structures are threatened; then an iridectomy should be performed. Melanomas of the iris, ciliary body, and angle require corneoscleral iridocyclectomy for removal. Dr. Cooper believes choroidal melanomas are best handled by enucleation when the fellow eye is normal. When a tumor develops in an only eye, less definitive measures are required. Currently, the application of radioactive cobalt plaques to achieve a dose of 10,000 to 12,000 rads at the apex of the tumor appears to be the best alternative. The therapy for retinoblastoma is, in many ways, similar. In biliateral cases, if all hope for useful vision in the poorer eye is lost, that eye is removed. The remaining eye, depending on the degree of involvement, is treated with 3,500 rads of radiation, photocoagulation to obliterate its blood supply, radioactive cobalt plaques (5,000 to 6,000 rads to the tumor apex), or chemotherapy (currently Cytoxan and vincristine).

Dr. Coleman found that ultrasonography is an invaluable aid in the evaluation and diagnosis of ocular and orbital tumors. In ophthalmoscopically visible intraocular tumors, ultrasound can reliably differentiate lesions with similar visual appearances. Of greater value is the ability of ultrasound to localize and characterize intraocular tumors obscured by such opacifications of the media as cataract, hemorrhage, or retinal detachment. Ultrasonography is of particular value in portraying soft tissue masses in the orbit, which cannot be evaluated by any other diagnostic technique. One can classify orbital tumors as to their size, location, degree of encapsulation, and sound transmission properties. Ultrasound can consistently differentiate neoplastic lesions from inflammatory orbital processes, thus allowing direct overall patient management.

In his second presentation, Dr. Brockhurst remarked that vitreous surgery includes injection of vitreous substitutes, manipulation, transvitreal diathermy coagulation, foreign body removal, and both open-sky and closed vitrectomy. Dr. Brockhurst felt vitrectomy now offers many new avenues of effective treatment for vitreous opacification and equatorial membrane formation that were formerly untreatable. However, complications are not uncommon and, since the procedures is new, the long-term effects are presently unknown. Because of this, one should not abandon time-proven, more established techniques unless these will clearly be ineffective without vitrectomy procedures.

Arnall Patz reported that precise resolution fluorescein angiography is a prerequisite in patient selection and in the photocoagulation treatment of patients with macular dis-

ease. Several methods were demonstrated to extrapolate fluorescein findings to the fundus view seen through the slit lamp and contact lens or with the ophthalmoscope. A useful landmark in the fluorescein angiogram is the avascular zone about the foveas, which in most, but not all patients is approximately 500 μ or one-third disk diameter in width. The blood column in a vein as it crosses the border of the optic disk is 125 μ wide. These two measurements can assist in precise localization of the new vessel membrane and aid in the selection of patients with subretinal neovascularization for photocoagulation. Dr. Patz emphasized that the true role of photocoagulation both in ocular histoplasmosis and senile macular degeneration requires documentation in carefully controlled studies.

A panel discussion with Frank W. Newell as moderator was the final offering at the conference.

The Clinical Conference of the Chicago Ophthalmological Society has been accredited for its Continuing Medical Education Program as of 1972 by the American Medical Association Council on Medical Education. This Continuing Medical Education activity is acceptable for 12 credit hours in Category I for the Physicians Recognition Award of the American Medical Association.

THOMAS CHALKLEY

AMERICAN JOURNAL OF OPHTHALMOLOGY

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Published monthly by the Ophthalmic Publishing Company
233 East Ontario St., Chicago, Illinois 60611

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THE IMPORTANCE OF HL-A ANTIGENS IN OPHTHALMOLOGY

Evidence linking histocompatibility (HL-A) antigens with various disease entities is being published with increasing frequency.[1-5] An individual inherits maternal and paternal genes that determine the histocompatibility complex. This complex consists of serologically and lymphocyte defined (SD and LD) antigens that are cell membrane determinants controlled by genes on chromosomes near the Ir genes regulating the immune response.[1,4,6,7] The membrane determinants exist on every nucleated cell, although they may not be equally abundant on all cells. Human leukocyte antigens (HL-A) gave the first SD series its name when the genetic locus was termed LA (locus A). Locus FOUR controls the second SD series of antigens and both series consist of many alleles. In addition to the strong LA and FOUR SD antigens, an individual's phenotype comprises a strong LD, as well as weaker SD and LD antigens (Figure).

Histocompatibility typing became more important as renal transplantation increased in frequency.[8] The antigens are under constant study and form the subject of yearly workshops where newly discovered SD and LD antigens are discussed, compared, and given official names. Corneal grafts have not stimulated undue immunologic problems. The success of the corneal graft appears to depend on factors other than histocompatibility antigens such as the surgeon's operative skill plus the use of immunosuppressive therapy (usually systemic or topical corticosteroids, or both).[9,10]

Vascularization and inflammation of the cornea bring leukocytes to the area. The "privilege of the cornea" may reflect the lack of encounter of the patient's lymphocytes with corneal proteins. They appear to become sensitized on exposure to cornea in the afferent arc of the immune response. Persistence or recurrence of corneal vascularization will bring antibody, antibody bearing, and lymphokine secreting lymphocytes to the cornea (the efferent arc of the immune response). At that time, anticorneal antibody,

which can diffuse into the cornea from immunity, may be important in the pathophysiology of chronic keratitis.[10-14] Similarly, vascularization may cause the histocompatibility antigens to become of greater importance in graft survival or rejection.[11]

In histocompatibility testing an individual's cells, usually peripheral lymphocytes, are tested with standardized antisera against the known SD allotypes of the LA and FOUR series.[1] Mixed lymphocyte cultures are performed by incubating an individual's lymphocytes with prepared stimulator cells to detect the LD antigens. The test can be inhibited by serum containing antibodies to SD loci although the cells remain viable. Mixed lymphocyte cultures can be linked to a host cell-donor relationship in which only cell contact reveals the membrane determinant. The brief description of the tests permits understanding of why an individual who has recently been transfused may have foreign cells in his circulation with SD and LD antigens, which will stimulate antibody secretion and cellular immunity.

HL-A antigens are not as strong antigenically as the A-B-O red blood cell antigens and rarely lead to anaphylactic reactions. Maternal sensitization to fetal antigens (paternally derived) provides many of the antisera used to test for SD antigens. Whether maternal antibodies to paternal fetal antigens affect the fetus is a matter of debate, particularly regarding infants with immune deficiency disease.[15]

The HL-A antigen is composed of two polypeptide chains. One chain has a molecular weight of 34,000, the other of 12,000. The latter is identical to β-2 microglobulin, which has an amino acid sequence resembling a

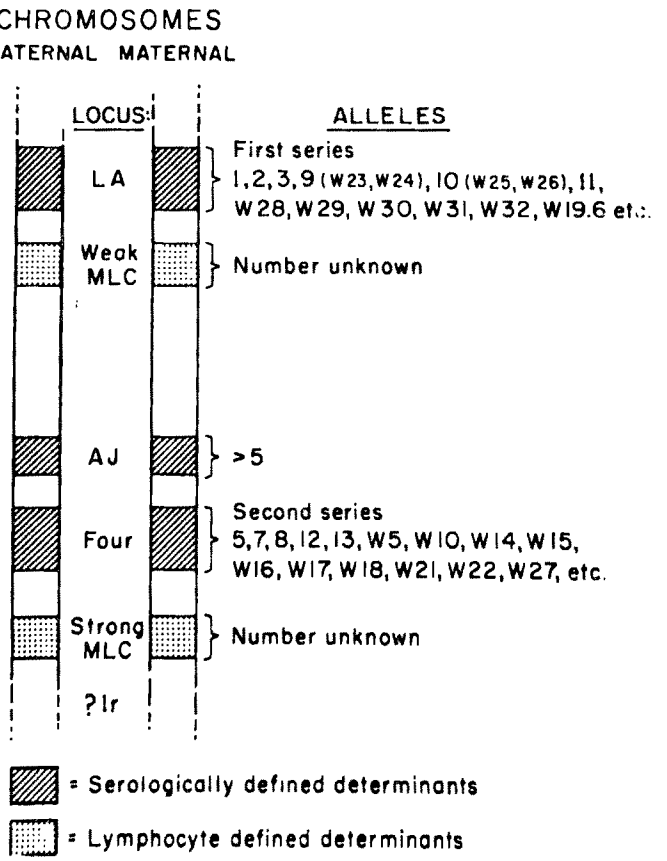


Figure (Henley and Leopold). Segment of chromosomes to indicate close relationship of histocompatibility genes and Ir gene. The exact location of Ir genes with respect to histocompatibility genes is not known. Nomenclature for the SD antigens controlled by the LA and FOUR loci was determined by the World Health Organization. HL-A initials are not indicated, only numbers are shown for established specificities. "W" designation is for new specificities, which originate in the yearly workshops and will be given an HL-A designation when thoroughly defined.

constant domain of the γ heavy chain of immunoglobulins.[16,17] The structure of the antigen recalls that of the immunoglobulin molecule and the close chromosomal relationship of the genetic loci for histocompatibility and the Ir gene.[1,4,6,7] The Ir gene does not control immunoglobulin structure but the type of immune response, that is, the class of antibody or the types of lymphokine secreted.

The association of some HL-A antigens with disorders attributed to aberrations of the immune response has led to worldwide research. Different population groups bear different HL-A antigens and it becomes critical to correlate not only the prevalence of certain HL-A antigens with disease states but also with their incidence in a similar population group.[18-20]

Refined statistical analytic methods have been outlined which take into consideration (1) the allotype's incidence in a strictly controlled normal population, (2) the association of SD allotypes controlled by the two stronger histocompatibility loci with each other, and (3) the mathematical correction for the number of allotypes tested.[1,3,5,21,22] An unpublished report by Aviner, Henley, Fotino, and Leopold outlines the meticulous statistical study which must be performed.

A group of disorders considered to be due to or associated with immunologic aberrations, as well as a variety of tumors, in particular lymphomas, have been studied critically.[1-5,23] The arthritides—ankylosing spondylitis, rheumatoid arthritis—are among the first group of diseases mentioned and are associated with HL-A 27.[7] This antigen may be of etiologic significance or it may permit an immune response leading to injury of these tissues and it may also be of importance in acute anterior uveitis.[24] Hereditary disorders, such as diabetes mellitus, have been carefully investigated and a strong association of HL-A8 or W15, or both, with juvenile insulin-dependent diabetes now seems to be established.[25-27] Whether the HL-A antigen renders this population more prone to (virus) infections that injure the islets of Langerhans, or whether the immune response in these patients makes them more susceptible to infectious damage of this tissue or whether the immune response itself is the cause of the injury is not known.[28]

A few patients and controls can demonstrate the reality of the association between disease and the HL-A serotype when it is strong, as is the case in ankylosing spondylitis and HL-A 27.[7] Problems of sampling are less important than in instances where the association is not so strong, as in a multifactorial hereditary disorder, such as open-angle glaucoma.[29-32] The same mechanisms listed for diabetes may be responsible. An increased incidence of some HL-A antigens compared to the normal population is inadequate to associate them with open-angle glaucomas.[33,34] One statistical analysis suggests an association of W5 with open-angle glaucoma (Aviner, Henley, Fotino, and Leopold, unpublished data).

The diagnosis of open-angle glaucoma is not always established in the same manner by different ophthalmologists. The findings presented in preliminary reports are not in agreement.[33,34] An intensive collaborative effort to link HL-A antigens with the presence of open-angle glaucoma appears justified. It should include susceptibility to the disorder, as detected by in vivo water provocation and steroid tests and other in vitro tests[35] (Aviner, Leopold, Okas, and Henley, unpublished data). In order to establish a large, heterogeneous patient population, cooperative studies among several university centers should evaluate not only the patient with open-angle glaucoma and the susceptible patient, but also his relatives in thorough family studies which will determine whether genes play a role in open-angle glaucoma. Similarly, a cooperative study may discern HL-A allotypes which may render patients more susceptible to the development of secondary intraocular hypertension.

WALTER L. HENLEY
IRVING H. LEOPOLD

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CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper; with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Sutureless Fasanella-Servat Blepharoptosis Correction

Editor:

The Fasanella-Servat procedure[1] introduced in 1961 is widely accepted for cases of minimal blepharoptosis if the levator function is good. Many modifications[2-6] in the original suturing technique have been offered to avoid the sometimes severe postoperative keratitis resulting from suture material abrading the cornea.

I recently discovered that the Fasanella-Servat operation can be performed without the use of any sutures and yet the good results obtained with this procedure have not been compromised. The essentials of my technique are as follows:

After everting the upper eyelid, approximately 0.5 ml of 2% lidocaine with epinephrine is injected subconjunctivally along the superior tarsal border. Two curved hemostats are placed in the standard manner[1,3-4] and allowed to remain tightly clamped for one minute. Straight, sharply pointed scissors is used to excise the tarsus by cutting in the center of the broad groove remaining in the tarsus after the removal of the hemostats. Bleeding, if any, is minimal and the cut ends of the tarsus and conjunctiva-Müller's muscle remain adherent. An antibiotic ointment is instilled and the eyelid is returned to its normal position. The eye is patched for 24 hours; a Frost suture is optional.

The maximal effect of this operation is apparent in three weeks although some elevation of the eyelid may be seen after 24 hours, depending on the extent of the tarsal resection, the severity of the blepharoptosis, and the amount of levator function.

The elimination of the suture prevents the only serious complication of the Fasanella-Servat procedure and further simplifies an already "simplified operation."[1]

Lewis Lauring, M.D.
San Francisco, California

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Nitrous Oxide Anesthesia With Gas in the Vitreous Cavity

Editor:

We wish to emphasize the danger of using nitrous oxide anesthesia when gas is present in the vitreous cavity. Since nitrous oxide is extremely soluble, it will diffuse rapidly into a body space containing a less soluble gas, thus causing rapid expansion of the gas pocket. Smith, Carl, Linn, and Nemoto in their article, "Effect of Nitrous Oxide on Air in Vitreous" (Am. J. Ophthalmol. 78: 314, 1974), reported a significant rise in intraocular pressure during nitrous oxide anesthesia in rhesus monkey eyes containing intravitreal air. The authors speculated that the increase in intraocular pressure if SF_6 were present in the vitreous cavity would be at least as great as that with intravitreal air. We have inadvertently documented this potential surgical hazard with intraocular SF_6.

A patient had a vitrectomy for a nonclear-

ing traumatic vitreous hemorrhage. A small sclerotomy site dialysis was treated by injection of a 2.25-ml mixture of 40% SF_6 and 60% air into the vitreous cavity. On the third postoperative day, a retinal detachment was discovered. A gas bubble occupying about 60% of the vitreous cavity was present. Intraocular pressure was normal and the anterior chamber was deep. The patient was returned to surgery for repair of the detachment. One hour after the start of anesthesia (prior to drainage or exoplant placement) the surgeon noted that the optic nerve was pale and the eye was firm. It was determined that the patient had been receiving continuous nitrous oxide at levels between 67% and 25%. This anesthetic agent was immediately discontinued and gas was aspirated from the eye. Fortunately the eye did well, but further delay in recognition of the problem could have resulted in permanent visual loss from ischemia of the retina and optic nerve.

If a patient with intraocular gas is returned to surgery, nitrous oxide should not be used as an anesthetic agent. In retinal detachment and vitreous surgery cases in which the gas is to be utilized, inhalation of nitrous oxide should be discontinued 10 or 15 minutes before the injection of gas.

DWAIN FULLER, M.D.
MAY LOU LEWIS, M.D.
Miami, Florida

REPLY

Editor:

I agree entirely with the recommendations of Drs. Fuller and Lewis, and for some time we have followed this routine at the Eye and Ear Hospital of Pittsburgh.

I have been watching for possible clinical problems with nitrous oxide with air in the vitreous. One interesting event is perhaps worthy of record.

A 5-year-old girl was admitted with a complete retinal detachment of the right eye. The eye was operated on under general anesthesia consisting of halothane, 60% nitrous oxide, and 40% oxygen. Subretinal fluid was drained and cryotherapy performed. Intravitreal air was then injected and more subretinal fluid expressed. The site of intraocular pressure (IOP) was found to be 71 mm Hg. Nitrous oxide was continued and the IOP was found to be 101 mm Hg within five minutes. Because of this rise, the nitrous oxide was discontinued and within a further six minutes the IOP was 66 mm Hg. There were no adverse affects in the eye from the transient rise in IOP.

In view of our experimental data, there is every reason to believe that this IOP change was associated with the intraocular diffusion of nitrous oxide.

R. BRIAN SMITH, M.D.
Pittsburgh, Pennsylvania

BOOK REVIEWS

CHORIORETINAL HEREDO-DEGENERATIONS. An Updated Report of La Société Française d'Ophtalmologie. By A. Franceschetti, J. François, and J. Babel. Springfield, Illinois, Charles C Thomas, 1974. Clothbound, 1371 pages, table of contents, index, 137 color plates, 897 black and white figures. $175

Starting in 1951 the French Ophthalmological Society presented an annual scientific report. Highlights are read at the annual meeting and shortly thereafter an encyclopedic review is published. These volumes are among the best in ophthalmology and provide the reader with a current erudite critique and review of permanent value.

The report in 1963 concerned chorioretinal heredodegenerations and appeared in two volumes of some 1,700 pages. It was prepared by Franceschetti of Geneva, François of Ghent, and Babel of Geneva, with the collaboration of A. DeRouck, P. Dieterle, S. Forni, D. Klein, A. Ricci, and Verriest. These volume were brilliantly prepared and constituted the foundation upon which many of the recent extensive advances in the study of hereditary diseases of the choroid and

retina were based. The volumes were soon translated into English and were rapidly out of print.

The present text is in English and brings the earlier report up to date. The authors are the same with the addition of A. T. Francheschetti, of Geneva, as a collaborator. The new volume supplements rather than replaces the earlier work. The references have been largely retained but brought up to date.

The bibliographies are comprehensive and essential to anyone seeking to review and describe hereditary abnormalities of the fundi. Many of the reviews have been rewritten and provide a systematic discussion rather than a listing of earlier reports as in the first volumes. An economy of words makes this edition some 300 pages shorter than the first. The 53 color plates of the first edition are retained and are beautifully reproduced. The book is highly recommended and is a must for all of those who manage hereditary and choroidal diseases.

FRANK W. NEWELL

OEIL ET CORTISONE. By Ph. Demailly, H. Hamard, and J.-P. Luton. Saint-Germain, Paris, Masson et Cie, Editeurs, 1975. Paperbound, 362 pages, table of contents, index, 158 black and white figures.

Vast experience with corticosteroids has been acquired throughout the world and much involves the ocular effects. With the cooperation of 17 others, Demailly, Hamard, and Luton have gathered, organized, and critically evaluated much of this worldwide information. To conserve space, only selected references are reviewed by the various authors. As in most previous reviews of this subject, the authors start with hypothalamic-hypophyseal-adrenal axis, then deal with the structure, actions, and regulation of the adrenocorticotropic hormone. In a historical fashion, they review the synthesis of cortisone, its transport, metabolism, biological, and metabolic effects. The metabolic effects of other corticosteroids on various tissues and systems of the body are summarized. In several chapters, the pharmacologic and physiologic function of the agents including ACTH and their side effects are dealt with in detail.

In specific fashion, the authors review the penetration of a variety of corticosteroids, particularly dexamethasone when topically applied as an acetate, alcohol, or phosphate preparation. This deals with experimental animal studies. Several chapters consider treatment of conjunctival, corneal, and uveal disorders including keratoplasties and scarring. During the course of these discussions, the role of corticosteroids as immunosuppressive agents is detailed and its comparison to other immunosuppressors evaluated. Specific attention is paid to the side effects of corticosteroids on glaucoma, lens, mucopolysaccharides of the angles, exophthalmos, and the neuro-ophthalmologic tissues.

This is a particularly good review for those who are knowledgable in French. For those limited to the English language, there are other publications that cover the information so well documented in this one. Interestingly, the opinions held by those working in the French-speaking countries are similar to those expressed independently in the United States. It is always helpful to review side effects and possible mechanisms for production. Perhaps by such a review, one can identify the specific cause of each of these side effects. This may lead to concepts for the development of agents free of these complications.

IRVING H. LEOPOLD

INNERE ERKRANKUNGEN UND AUGE. By Andreas Heydenreich. Leipzig, VEB Georg Thieme, 1975. Clothbound, 310 pages, table of contents, index, 106 black and white figures. $25.80

This is a short book that contains in an

abbreviated form a summary of various eye signs and symptoms in systemic diseases. These signs and symptoms are presented in tables or as abbreviated highlights.

While there is no attempt made to cover any topic in depth, the summary-like presentation may be useful for medical students and residents. The bibliography is adequate though in general it does not go beyond 1970.

Some of the modern developments of many of the conditions are not considered, but the older literature is certainly well summarized. The book also contains some chapters on neuro-ophthalmology, the metastases of ocular tumors, and toxic effects on the eye.

The differential diagnostic tables at the end of the book may be of some benefit to medical students.

FREDERICK C. BLODI

PEDIATRIC OPHTHALMOLOGY. By Robison D. Harley. W. B. Saunders Co., 1975. Clothbound, 1112 pages, table of contents, index, 877 black and white figures, 14 color plates. $55

Dr. Harley initiated the cooperation of some 40 eminent ophthalmologists, pediatricians, dermatologists, radiologists, anesthesiologists, and the like who presently or were in the past associated with Wills Eye Hospital to write this text on pediatric ophthalmology. It is all-encompassing, touching such diverse subjects as anesthesiology of the child and education of the visually handicapped, dental changes and pediatric syndromes, tumors, and trauma. The book is addressed to the resident and to the practicing ophthalmologist. It gives excellent photographic and schematic presentations. Most sections are extensively referenced and help the interested to find recent screened relevant literature. Wide use has been made of tabulations correlating ocular abnormalities with systemic findings. These tables should prove very useful for the practicing pediatric ophthalmologist worried about syndrome identification or in case syndrome identification has been made about extraocular complications. The book extensively refers to inherited ocular and systemic diseases with ocular complications. Here, unfortunately, many omissions occur and throughout the book, the description of syndromes—their inheritance, systemic manifestations—are inaccurate in many instances.

The basic context of the book—its orientation, the material included, its comprehensiveness—should prove useful for the student as well as the practitioner. However, there are evident shortcomings in nosology and clinical descriptions, which definitely limits the usefulness of this book.

IRENE H. MAUMENEE

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

ALBRECHT VON GRAEFES ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE OPHTHALMOLOGIE

THE INFLUENCE OF TOPICALLY APPLIED BETHANIDINE ON INTRAOCULAR PRESSURE AND PUPIL IN THE RABBIT. Krieglstein, G. K. (Univ. Eye Hosp., Würzburg, West Germany). Albrecht von Graefes Arch. Klin. Ophthalmol. 196:31, 1975.

Bethanidine is an adrenergic blocking agent with a chemical structure and pharmacologic properties similar to guanethidine. These compounds inhibit the release of noradrenaline during stimulation of the adrenergic nerve and sensitize the effector cells of exogenous catecholamines. Bethanidine appears to be more potent than guanethidine in blocking the adrenergic nerve, more rapid in onset with a shorter duration of action. In this study bethanidine was used in 0.5%, 1.0%, 2.0% and 5.0% in one eye of a series of rabbits. In all cases there was a decrease in pressure in the eye treated as compared to the control eye but in the 1.0% and 2.0% solutions there was also a decrease in the control eye, probably because of systemic absorption. No significant pupillary reactions were found with the use of bethanidine. (5 figures, 1 table, 18 references)—David Shoch

NEONATAL HERPES SIMPLEX RETINITIS. Cibis, G. W. (Univ. Iowa, Iowa City, Ia.). Albrecht von Graefes Arch. Klin. Ophthalmol. 196:39, 1975.

Pathologic material from an acute case of neonatal herpes simplex retinitis is presented. There was marked necrosis of all retinal layers including the pigment epithelium. Choroid and vitreous appeared only secondarily involved. The retinal necrosis was sharply delineated stopping at the ora serrata. This is interpreted as being more compatible with an immunologically determined process than with direct infection. Indirect evidence for this viewpoint is the failure to find any evidence of virus in the retina, such as inclusion bodies, by electron microscopy or by fluorescent antibody staining. (9 figures, 13 references)—Author's abstract

POSTOPERATIVE ASTIGMATISM AFTER PENETRATING CORNEAL GRAFTS. (German) Schwobel, W. (Univ. Eye Clinic, Zurich, Switzerland). Albrecht von Graefes Arch. Klin. Ophthalmol. 196:61, 1975.

The postoperative astigmatism was compared in 71 patients who had transplants performed for keratoconus with 47 patients who had transplants performed for other reasons. The postoperative astigmatism in keratoconus patients was greater than in other types of corneal disease by about a diopter. The average for the 47 general cases being 5.03 diopters and in keratoconus 6.0 diopters. On the other hand there seemed to be very little difference between large and small grafts or between running sutures or interrupted sutures. (7 figures, 4 tables, 10 references)—David Shoch

ULTRASTRUCTURAL FEATURES OF POSTERIOR VITREOUS DETACHMENT. Foos, R. Y. (Jules Stein Eye Inst. UCLA School Med., Los Angeles, Calif.). Albrecht von Graefes Arch. Klin. Ophthalmol. 196:103, 1975.

Although the entity of posterior vitreous detachment has been studied for some time, it has not been definitively established as to where this detachment occurs. By the use of the electron microscope, the author found that the detachment occurs at the anatomical vitreoretinal junction between the inner limiting lamina of the retina and the vitreous cortex. The surface of the lamina remains smooth without vitreous residues attached to it. (9 figures, 22 references)—David Shoch

SIGNS, THERAPY AND FOLLOW-UP OF CASES WITH PURE BLOW-OUT FRACTURES OF THE ORBIT. (German) Herzau, V. (Univ. Eye Clinic, Tübingen, West Germany). Albrecht von Graefes Arch. Klin. Ophthalmol. 196:143, 1975.

Twenty-nine patients with blow-out fractures of the orbit formed the basis for this study. Ten of the patients normalized spontaneously within two weeks. Nineteen required surgery on the basis of two criteria: diplopia

and a positive traction test, not resolving within ten days and large herniations into the antrum. It is important to note that in spite of this, normalization was achieved in only eight of the 19 patients. (9 figures, 1 table, 7 references)—David Shoch

Annales d'Oculistique

THE PROGNOSTIC FACTORS OF THE IRVINE-GASS SYNDROME. (French) Bonnet, M. (Red Cross Hosp., Lyon, France). Ann. Ocul. 208:275, 1975.

Twenty-two eyes (17 patients) which showed the Irvine-Gass syndrome after cataract extraction were followed from one to five years. The macular edema lasted more than a year in 60% of the cases. At the conclusion of the period of observation, visual acuity was good in 60% of the cases and rather poor in 40%. The functional prognosis is largely conditioned by the duration of the macular edema. It is good for those in which the edema only lasts for a few months and is much poorer when the edema lasts more than a year. Of particular interest is the fact that 22% of the patients in this series eventually turned up with a rhegmatogenous detachment of the retina. (7 references)—David Shoch

Archives d'Ophtalmologie

ALTERATIONS IN COLLAGEN IN CORNEAL DEGENERATIONS. (French) Babel, J. (Geneva, Switzerland). Arch. Ophtalmol. 35:39, 1975.

The author studied the various corneal degenerations with both light and electron microscopy and feels that alterations in collagen in the dystrophies are secondary and not the primary cause of the dystrophy. In general the dystrophies appear to be a result of abnormalities of the keratocytes or of the epithelial cells of the cornea. Changes in collagen do occur, for example in Fuchs' dystrophy, but it is likely that these are secondary. The only disease in which there is a primary degeneration of the tissue collagen is keratoconus. (6 figures, 16 references)—David Shoch

REGENERATION OF CORNEAL ENDOTHELIUM IN THE RABBIT. (French) Hirsch, M., Faure, J., Marquet, O., and Payrau, P. (Ctr. Ophthalmic Research, Paris). Arch. Ophtalmol. 35:269, 1975.

A central area of cornea of rabbits, 1 centimeter in diameter, was frozen for ten minutes by means of liquid nitrogen. The endothelium was then studied daily by means of flat preparation techniques. The corneal thickness was also measured and an estimation made of the transparency. By the fifth day Descemet's membrane was entirely covered by regenerating endothelium and from this time on the thickness and transparency of the stroma became normal. It is obvious that regenerated endothelial cells do quickly regain their specific function of acting as a barrier against hydration of the stroma. (5 figures, 2 tables, 9 references)—David Shoch

Archives of Ophthalmology

IRIS ANGIOGRAPHY IN CYSTOID MACULAR EDEMA AFTER CATARACT EXTRACTION. Kuhtow, M., and Hendrickson, P. (Klin. Inst. Experimentelle Ophthalmol. Bonn, West Germany). Arch. Ophthalmol. 93:187 1975.

Iris angiography was performed on eight patients (nine eyes), who had cystoid macular edema postcataract extraction. The fundus fluorescein angiographies showed typical star shaped, multiloculated staining of the macular area. The iris angiographies demonstrated moderate to massive leakage of dye from the iris, and possibly leakage of ciliary body vessels into the anterior chamber, thus evidencing the until now suspected but undocumented fact that fluorescein leakage is not restricted to the fundus vessels. These data tend to support the idea that this type of macular edema is due to a vascular abnormality, and not to altered vitreous mechanics. (15 figures, 13 references)—Authors' abstract

POLYGLYCOLIC ACID SUTURE IN STRABISMUS SURGERY. Blau, R. P., Greenberg, S., Lorfel, R., and Sugar, H. S. (Dept. Ophthalmol., Sinai Hosp. Detroit, Detroit, Mich.). Arch. Ophthalmol. 93:538, 1975

Polyglycolic acid, synthetic, absorbable, braided suture was compared to gut with respect to handling, strength, and tissue reacti-

in 70 strabismus procedures. This new suture material produced less tissue reaction than gut and had handling characteristics that were similar to silk. It can be used in smaller sizes than gut because of its greater strength and firm knot. Polyglycolic acid suture appears to be a useful addition to ophthalmic suture materials. (6 figures, 2 tables, 13 references)—Authors' abstract

Australian Journal of Ophthalmology

AUTOMATIC TEAR-DELIVERY SPECTACLES—RECENT ADVANCES. Flynn, F. (Port Moresby, Papua New Guinea). Aust. J. Ophthalmol. 3:73, 1975.

Spectacles are used to carry a device for the treatment of aqueous lacrimal deficiency. It is simple with a gravity activated flow from two reservoirs in the side arm of the spectacles, via hidden tubes to the medial canthi. Full details and clear photographs are presented. The substitute tears are delivered to the conjunctival sac in a continuous imperceptible ooze. Flow may be regulated according to variations in atmospheric conditions. (7 figures, 16 references)—Ronald Lowe

Experimental Eye Research

RETINAL NEW VESSEL FORMATION FOLLOWING EXPERIMENTAL VEIN OCCLUSION. Hamilton, A. M., Marshall, J., Kohner, E. M., and Bowbyes, J. A. (Hammersmith Hosp., London). Exp. Eye Res. 20:493, 1975.

After occlusion of the superior and inferior temporal veins of a mature rhesus monkey by argon laser application, the authors performed fluorescein angiography at two week intervals and enucleated the eye after five months. Progressive revascularization of the retina by abnormal capillaries was demonstrated throughout the period of observation and, on electron microscopy, three distinct types of capillaries were identified. This is the first mature animal model of experimental venous occlusion. (4 figures, 9 references)—Barton L. Hodes

THE FINE STRUCTURE OF THE TRABECULAR MESHWORK AT GRADED LEVELS OF INTRAOCULAR PRESSURE (1) PRESSURE EFFECTS WITHIN THE NEAR-PHYSIOLOGICAL RANGE (8 TO 30-MM HG). Grierson, I., and Lee, W. R. (Tennent Instit. Ophthalmol., Univ. Glasgow, Glasgow, U.K.). Exp. Eye Res. 20:505, 1975.

The outflow apparatus from rhesus monkeys which had been subjected to graded levels of intraocular pressure (8 to 30 mm Hg) was studied by transmission electron microscopy. At the higher pressures marked distension of the outer corneoscleral and the endothelial layers of the meshwork occurred, but cell-to-cell contact across the intertrabecular spaces and in the endothelial meshwork was maintained by extended endothelial cell processes. The elasticity of the native cells was attributed to the presence of abundant intracytoplasmic microfilaments. "Button" junctions were observed at the sites of process apposition and these were considered to be an important factor in the cellular adhesion. The endothelium lining the trabecular aspect of Schlemm's canal remained in close contact with the underlying meshwork throughout the pressure range and cellular rather than extracellular contacts were thought to be the major anchoring mechanism. With increase in intraocular pressure, there was an apparent decrease in extracellular material in the endothelial meshwork. A statistical analysis demonstrated a significant increase in the counts of lysosomes, lysosome complexes, multivesicular bodies and lipid vesicles in the meshwork cells at 30 mm Hg when compared to the counts at 15 mm Hg (the control pressure). (16 figures, 15 references)—Authors' abstract

THE FINE STRUCTURE OF THE TRABECULAR MESHWORK AT GRADED LEVELS OF INTRAOCULAR PRESSURE (2) PRESSURES OUTSIDE THE PHYSIOLOGICAL RANGE (0 AND 50 MM HG). Grierson, I., and Lee, W. R. (Tennent Institute Ophthalmol., Univ. Glasgow, Glasgow, U.K.). Exp. Eye Res. 20:523, 1975.

The effects of 60 min exposure to high (50 mm Hg) and low (0 mm Hg) intraocular pressure in the outflow apparatus of the rhesus monkey have been assessed by transmission electron microscopy. At high pressure there is marked distension of the endothelial and outer

corneoscleral parts of the meshwork with occlusion of the anterior part of Schlemm's canal, but in this region cellular integrity is maintained. In the posterior part of the meshwork, intercellular connections are disrupted and degenerative changes are observed in the trabeculae. At 0 mm Hg intraocular pressure, the outer half of the meshwork is bowed inwards and compressed, and degeneration of the lining cells and trabecular cores is progressively advanced toward the inner meshwork. The graded preservation of the meshwork is attributed to diffusion of oxygen from the packed erythrocytes in the dilated canal of Schlemm. (7 figures, 6 references)—Authors' abstract

Investigative Ophthalmology

QUANTITATIVE GUIDELINES FOR EXOTROPIA SURGERY. Scott, A. B., Mash, A. J., and Jampolsky, A. (Smith-Kettlewell Inst. Visual Sciences, San Francisco, Calif.). Invest. Ophthalmol. 14:428, 1975.

In an attempt to establish preoperative guidelines for exotropia surgery, 58 patients with exotropia who were followed for 7 +/− 2 months postoperatively were statistically analysed to determine the amount of change in exodeviation per mm surgery performed. Bilateral lateral rectus recessions (BLR) were performed for 30 patients, while recession of the lateral and resection of the medial of the same eye (R + R) were done for 28 patients. Mathematical formulae are presented to assist in determining preoperatively the amount and type (BLR vs. R + R) of surgery to be undertaken for exodeviations. (2 figures, 8 tables, 13 references)—Barton L. Hodes

Journal of Pediatric Ophthalmology

LEUKEMIC INVOLVEMENT OF THE OPTIC NERVE. Rosenthal, A. R., Egbert, P. R., Wilbur, J. R., and Probert, J. C. (Dept. Ophthalmol., Stanford Univ., Stanford, Calif.). J. Pediatr. Ophthalmol. 12:84, 1975.

Five cases of leukemic infiltration of the optic nerve in children have been reported. One child had chronic myelogenous leukemia while four had variants of acute lymphoblastic leukemia. In two, in whom no treatment was instituted, histopathology revealed primarily leukemic involvement of the optic nerve head. Three other cases involving four eyes (two eyes with primarily optic nerve head infiltration and two eyes with primarily retrolaminar infiltration and severely decreased visual acuity) were treated with approximately 2000 rads to the orbit over a one to two week period with complete resolution of the clinical pathology and return of visual acuity to normal. Subsequent histopathological examination of these eyes revealed no leukemic involvement of the nerve head or retrolaminar nerve. Local radiation is recommended as an effective treatment modality for visual loss secondary to optic nerve involvement in acute leukemia. (7 figures, 10 references)—Authors' abstract

CONGENITAL CATARACT AND MATERNAL STEROID INGESTION. Kraus, A. M. (Buffalo, N.Y.). J. Pediatr. Ophthalmol. 12:107, 1975.

A case of congenital cataracts associated with maternal steroid ingestion is presented. Although the association may be fortuitous, the report was deemed worthwhile, as certainly there is circumstantial evidence that the relationship may be causal. (2 figures, 2 references)—Author's abstract

Klinische Monatsblätter für Augenheilkunde

BLOCK EXCISION OF INTRAOCULAR TUMORS. (German) Naumann, G. (Univ. Eye Clinic, Hamburg, West Germany). Klin. Monatsbl. Augenheilkd. 166:436, 1975.

Twelve tumors of the anterior uvea were excised in block fashion, removing the ciliary body, peripheral choroid and adjacent cornea, sclera, iris and retina in a single block. Of these tumors, nine were malignant melanomas and one a melanocytoma. In five of the cases the lens were removed at the same time and in ten of them a vitrectomy was also necessary. In general the visual results were quite poor because of cataract formation, hemorrhages into the vitreous but the globe was retained in 11 of the 12 cases. (7 figures, 1 table, 29 references)—David Shoch

PIGMENTARY GLAUCOMA. SCANNING ELECTRON MICROSCOPE FINDINGS. (German) Hoffman, F., Dumitrescu, L. ,and Hager, H. (Steglitz Eye Clinic, Berlin, Germany). Klin. Monatsbl. Augenheilkd. 166:609, 1975.

Trabeculectomy was performed on both eyes of a patient with pigmentary glaucoma. Examination of the specimens with an electron microscope showed the intertrabecular spaces were largely blocked by pigment granules which in some places were stored in the clump cells of the iris. The authors feel that it is the pigment that blocks the drainage of aqueous humor and causes the rise in pressure in spite of wide iridocorneal angles. (4 figures, 24 references)—David Shoch

HEMOGLOBINOPATHIES IN OPHTHALMOLOGICAL PRACTICE. (German) Rummeld, R. (Univ. Eye Clinic, Düsseldorf, West Germany). Klin. Monatsbl. Augenheilkd. 166:644, 1975.

The hemoglobinopathies have many eye signs and the author lists some of the diseases of the eye that are caused by changes in hemoglobin. These range from sludging phenomena in the conjunctiva to capillary thrombosis in the ciliary body resulting in paralysis of accomodation, peripheral uveitis, arteriovenous aneurysms, neovascularization of the retina and secondary retinal detachments. A finding of any of these entities should alert one to the possibility of a hemoglobin anomaly. (4 figures, 37 references)—David Shoch

MALIGNANT MELANOMA OF THE IRIS—23 YEARS AFTER INCOMPLETE INCISION OF TUMOR. (German) Freyler, H. (Univ. Eye Clinic, Vienna, Austria). Klin. Monatsbl. Augenheilkd. 166:704, 1975.

A malignant melanoma of the iris was excised from the eye of a 54-year-old man. Twenty-three years later he developed absolute glaucoma and the eyeball was excised. The same type of tumor was found in the chamber angle, in the ciliary body around scleral blood vessels and subconjunctivally. However, there was no evidence of any metatases throughout the 23 years or at the present time. The tumor was entirely confined to the eye. (5 figures, 12 references)—David Shoch

TRANSACTIONS OF THE AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

EVALUATION OF CLOSED-CIRCUIT TELEVISION AS AN OPTICAL AID FOR THE LOW-VISION PATIENT. Fonda, G. E., Thomas, H., and Schnur, R. (St. Barnabas Med. Ctr., Livingston, NJ). Tr. Am. Acad. Ophthalmol. Otolaryngol. 79:468, 1975.

Of 75 patients with reduced visual acuity only 15 were happy with the use of a closed-circuit television as an optical aid. The usefulness of the device varies inversely with the visual acuity. Patients with 20/200 or better prefer to use hand-held magnifiers and other portable devices. When the vision gets down to 20/400 or less, then apparently there is enough improvement to warrant the use of a non-portable, expensive device. Closed-circuit television is worth trying as an optical aid for a limited number of patients with very poor vision. (1 figure, 2 tables, 3 references)—David Shoch

AUTOMATIC REFRACTIONS, A SYMPOSIUM. Rubin, M. L. (Dept. Ophthalmol. Univ. Florida Med. Ctr., Gainesville, Fla.). Tr. Am. Acad. Ophthalmol. Otolaryngol. 79: 481, 1975.

The important point to be gained from a perusal of the articles in this symposium is that objective refractometry can actually only replace retinoscopy. It is replacing one theoretically objective technique by another. One cannot use the output of the objective refractometer as described in these articles to yield a prescription which can simply be turned over to an optician to grind out a pair of spectacles. For optimal results the objectively determined findings must be refined with a subjective refraction. The objective data from the machine should be treated simply as additional information to help with the usual refraction. The reason for this is that there is a rather broad image zone in which the patient chooses a particular point which is best for him. The machine cannot pick this point. Therefore, objective refractometry must be checked by the patient's subjective responses.—David Shoch

GREATER OCCIPITAL NEURALGIA: AN OCULAR PAIN SYNDROME WITH MULTIPLE ETIOLO-

GIES. Knox, D. L., and Mustonen, E. (Wilmer Ophthalmol. Inst., Johns Hopkins Hosp., Baltimore, Md.). Tr. Am. Acad. Ophthalmol. Otolaryngol. 79:513, 1975.

The greater occipital neuralgia syndrome should be suspected in patients, usually women, who complain of ocular, orbital, or temple pain for which no cause can be found. Patients will have either no local disease or ocular problems not usually associated with pain. Pressure on the greater occiptal nerves may elicit exquisite tenderness and reproduce the referred pain in eye, orbit, or temple. Therapy is directed at reducing posterior neck muscle tension and painful stimuli from the irritated nerves. Local anesthetic injections with or without soluble corticosteroid give dramatic relief. (2 tables, 17 references)—Authors' abstract

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received at least three months prior to the date of occurrence.

XI PAN AMERICAN CONGRESS OF OPHTHALMOLOGY

The XI Pan American Congress of Ophthalmology will be held in Santiago, Chile, March 20-25, 1977. For further information, write Juan Verdaguer, Jr., M.D., Casilla 16197, Santiago 9, Chile.

RETINA FOUNDATION: INTERNATIONAL TRAUMA CONGRESS

The Eye Research Institute of Retina Foundation will hold a three-day congress in Boston, June 17-19, 1976. Recent advances in the diagnosis and management of trauma of the anterior and posterior segment will be discussed. For further information, write H. MacKenzie Freeman, M.D., Eye Research Institute of Retina Foundation, 20 Staniford St., Boston, MA 02114.

WILMER OPHTHALMOLOGICAL INSTITUTE: SECOND ANNUAL SYMPOSIUM ON FLUORESCEIN ANGIOGRAPHY AND THE MACULA

The Retinal Vascular Service of the Wilmer Ophthalmological Institute will hold the second annual symposium on fluorescein angiography and the macula, Jan. 26 and 27, 1976, at the Wilmer Institute, Baltimore. The program is approved for 16 hours of AMA credit as a continuing education course, Category I. For further information, write Miss Peggy Rasnake, Secretary to Dr. Stuart L. Fine, Wilmer Institute, Johns Hopkins Hospital, 601 N. Broadway, Baltimore, MD 21205.

GERMAN OPHTHALMOLOGICAL SOCIETY: INTERNATIONAL SYMPOSIUM

The German Ophthalmological Society will sponsor an international symposium, "Intraocular foreign bodies and metallosis," March 30-April 2, 1976. For further information, write Prof. Dr. H. Neubauer, D-5000 Köln 41, Universitäts-Augenklinik, Joseph-Stelzmann-Str. 9, Germany.

SIXTH AFRO-ASIAN CONGRESS OF OPHTHALMOLOGY

The Sixth Afro-Asian Congress of Ophthalmology will be held in Madras, India, Jan. 4-8, 1976. For further information, write Dr. J. Agarwal, Organizing Secretary, 29C. Edward Elliots Rd., Madras-4, India.

SCHEIE EYE INSTITUTE: BICENTENNIAL CONGRESS

The Scheie Eye Institute will hold a Bicentennial Congress on Ophthalmic Surgery in Philadelphia, May 9-13, 1976. The fee for the congress is $300. For information, write James A. Katowitz, M.D., Scheie Eye Institute, 51 N. 39th St., Philadelphia, PA 19104.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY: SOUTHERN REGIONAL MEETING

The Association for Research in Vision and Ophthalmology will hold its southern regional meeting in Houston, Texas, Nov. 7 and 8, 1975. For further information, write Gunter K. von Noorden, M.D., Professor of Ophthalmology, Baylor College of Medicine, Houston, TX 77025.

RUDOLPH ELLENDER MEDICAL FOUNDATION, INC.: 16TH ANNUAL INSTRUCTION COURSE

The Rudolph Ellender Medical Foundation, Inc., will hold the 16th annual instructional course in contact lens fitting March 4-6, 1976, in New Orleans. The course has been approved by the AMA as a Continuing Course in Medical Education, Category I.

EMORY UNIVERSITY: POSTGRADUATE COURSE

The Department of Ophthalmology of Emory University School of Medicine will present a postgraduate course, "Modern concepts of anterior segment surgery," Dec. 4 and 5, 1975, in Atlanta, Georgia. Registration fee for practitioners is $125. For further information and application forms, write F. Phinizy Calhoun, Jr., M.D., 1365 Clifton Rd., N.E., Atlanta, GA 30322.

WILLS EYE HOSPITAL: COURSE ON MANAGEMENT OF CORNEAL AND EXTERNAL DISEASES

The Cornea Service at Wills Eye Hospital will

present a course on management of corneal and external diseases Dec. 12 and 13, 1975, at the Marriott Hotel, City Line Avenue, Philadelphia, Pennsylvania. The registration fee is $150 and includes luncheons and banquet. Checks should be made payable to Corneal Conference. For information and registration, write Peter R. Laibson, M.D., Director, Cornea Service, Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130. The course is accredited in Category I of the American Medical Association.

University of Alabama: Annual Symposium

The Combined Program in Ophthalmology, The Eye Foundation Hospital, and the University of Alabama in Birmingham, will hold their annual symposium, "Perspectives in ophthalmology," Dec. 5 and 6, 1975, at the Hyatt House, Birmingham, Alabama. Guest faculty includes Crowell Beard, Ronald Carr, Claes Dohlman, Nicholas Douvas, Eugene Helveston, Howard Joondeph, Charles Kelman, Karl Ossoinig, Charles L. Schepens, Robert Shaffer, J. Lawton Smith, Stephen Trokel, Lorenz Zimmerman, and H. Christian Zweng. Registration fee, payable to the Combined Program in Ophthalmology, is $150 for practicing ophthalmologists, $35 for residents, fellows, and active-duty military personnel. For further information, write: Harold W. Skalka, M.D., 1720 8th Ave. South, Birmingham, AL 35233.

University of Oklahoma Health Sciences Center: Symposium

The University of Oklahoma Health Sciences Center of Ophthalmology and the Dean A. McGee Eye Institute will present a dedication symposium, "Current concepts in ophthalmology," Dec. 2 and 3, 1975. Topics include anterior segment surgery, phacoemulsification, intraocular lenses, strabismus, glaucoma, cornea, neuro-ophthalmology, practical plastic procedures, current and future ophthalmic research. For further information, write Caroline Cannon, Dean A. McGee Eye Institute, 800 N.E. 15th, Suite 421, Oklahoma City, OK 73104.

Cleveland Clinic Foundation: Postgraduate Seminar

The Department of Ophthalmology, Cleveland Clinic Foundation, will hold a postgraduate seminar Dec. 3 and 4, 1975. Symposia topics include: "Lacrimal disease and surgery." "Surgical management of blepharoptosis," and "Practical clinical aspects of glaucoma." For further information and application forms, write Education Department, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44106.

Personal

Steven G. Kramer

Steven G. Kramer has been named professor and chairman of the Department of Ophthalmology at the University of California San Francisco School of Medicine to succeed Michael J. Hogan. Dr. Kramer received his undergraduate degree and his Ph.D. from the University of Chicago. He received his M.D. from Western Reserve University. He served an internship at the University of Chicago Hospitals and Clinics where he became chief resident and instructor in ophthalmology. He served as chief of the Ophthalmology Service at Madigan Army Medical Center, Tacoma, Washington, before being appointed chief of ophthalmology, Veterans Administration Hospital, San Francisco, and assistant clinical professor and vice chairman of ophthalmology at the University of California San Francisco School of Medicine.

FIVE-YEAR OPHTHALMIC MEETING CALENDAR

For listings, write Bruce E. Spivey, M.D., Professor and Chairman, Pacific Medical Center, Department of Ophthalmology, P.O. Box 7999, San Francisco, CA 94120.

1975

NOVEMBER	2-6	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
	12-15	International Symposium on Cataracts	Iowa City
	29-DEC. 4	American Medical Association, Clinical Convention	Honolulu

1976

JANUARY	4-6	VI Afro-Asian Congress of Ophthalmology	Madras, India
	6-15	Dedication, new facilities, Bascom Palmer Eye Institute	Miami
	17	American Board of Ophthalmology (written)	Multiple sites
		Ophthalmic Knowledge Assessment Program, AAOO (written)	Multiple sites
MARCH	24-26	The Czechoslovak Ophthalmological Society	Prague, Czechoslovakia
APRIL	5-9	European Congress of Ophthalmology	Hamburg, Germany
	28-May 1	II World Congress on the Cornea	Washington, D.C.
MAY	7-10	American Board of Ophthalmology (oral)	Philadelphia
	14-16	American Ophthalmological Society	Kilauea, Hawaii
	16-21	Pacific Coast Oto-Ophthalmological Society	Seattle
JUNE	13-19	Club Jules Gonin Meeting	Lausanne, Switzerland
	26-JULY 1	American Medical Association, Annual Convention	Dallas
AUGUST	8-13	Asia Pacific Academy of Ophthalmology	Denpasar, Bali, Indonesia
SEPTEMBER	12-16	American Academy of Ophthalmology and Otolaryngology	Las Vegas (tentative)
OCTOBER	11-15	American College of Surgeons, Clinical Congress	Chicago
	21-24	American Board of Ophthalmology	San Francisco
NOVEMBER	11-15	Association of American Medical Colleges	San Francisco
DECEMBER	2-5	American Board of Ophthalmology (oral)	Chicago
	4-8	American Medical Association Clinical Convention	Philadelphia

1977

MARCH	20-25	XI Pan American Congress of Ophthalmology	Santiago, Chile
APRIL	24-28	Pacific Coast Oto-Ophthalmological Society	Tucson, Arizona
	26-30	Association for Research in Vision and Ophthalmology	Sarasota, Florida
MAY	4-7	American Board of Ophthalmology (oral)	San Francisco
	15-20	Instituto Barraquer VII International Course	Barcelona
	30-JUNE 1	American Ophthalmological Society	Hot Springs, Virginia
JUNE	18-23	American Medical Association Annual Convention	San Francisco
SEPTEMBER	10-11	International Intra-ocular Implant Society	Coronado, California
OCTOBER	16-19	American Board of Ophthalmology (oral)	Philadelphia
	17-21	American College of Surgeons Clinical Congress	Dallas
NOVEMBER	6-10	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
DECEMBER	4-7	American Medical Association, Interim Convention	Chicago

1978

MAY	14-21	International Congress of Ophthalmology—Concilium Ophthalmologicum Universale	Kyoto, Japan
	29-31	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	16-20	American College of Surgeons Clinical Congress	San Francisco
NOVEMBER (tentative)	5-9	Association of American Medical Colleges	New Orleans

1979

MAY	28-30	American Ophthalmological Society	Washington, D.C.
OCTOBER	22-26	American College of Surgeons Clinical Congress	Hot Springs, Virginia
NOVEMBER	4-8	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Chicago

New Orleans Academy of Ophthalmology

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Professor, Department of Ophthalmology
Bascom Palmer Eye Institute
University of Miami School of Medicine
Miami, Florida

FRANCIS A. L'ESPERANCE, M.D.
Assistant Professor of Clinical Ophthalmology
Edward S. Harkness Eye Institute
Columbia University College of Physicians and Surgeons
New York, New York

RUDOLF KLOTI, M.D.
Clinical Assistant Professor of Ophthalmology
University Eye Clinic
Zurich, Switzerland

ROBERT MACHEMER, M.D.
Associate Professor
Department of Ophthalmology
Bascom Palmer Eye Institute
University of Miami School of Medicine
Miami, Florida

J. WALLACE McMEEL, M.D.
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Harvard Medical School
Boston, Massachusetts

ARNALL PATZ, M.D.
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and The Seeing Eye Research Professor
Wilmer Ophthalmological Institute
The Johns Hopkins Hospital
Baltimore, Maryland

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Tuition is $600.00. For further information and application forms, please write: Richard S. Ruiz, M.D. Director of the Program in Ophthalmology, 1121 Hermann Professional Building, Houston, Texas 77025, A/C 713, 526-7261.

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Here are some of the subjects we will be covering for you: examination methods, pupils, optic neuritis, headaches and diplopia.

Dates:	November 6 and 7, 1975
Place:	Houston, Texas Marriott Motor Hotel
Instructors:	J. Lawton Smith, M.D. Miami, Fla. J. A. McCrary III, M.D. Houston, Tx.
Fee:	$125.00 ($25.00 for residents)

For additional details write: Office Neuro-ophthalmology Course, J. A. McCrary III, M.D., Dept. of Ophthalmology, Baylor College of Medicine, Houston, Tx. 77025.

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presents

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Cataract Surgery
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Medical and Surgical
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Sponsored by the Combined Program in Ophthalmology, The Eye Foundation Hospital and The University of Alabama in Birmingham. Co-sponsored by the Milton Roy Company, Sarasota, Florida.

This continuing medical education offering meets the criteria for 14½ hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association.

REGISTRATION FEE
$150 for Practicing Ophthalmologists
$35 for Residents, Fellows and active duty military personnel with letter from program director.

DECEMBER 5, 1975
REGISTRATION—7:30 A.M.
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REGISTRATION—7:45 A.M.
Approximately 30 major ophthalmic firms have technical exhibits

Place:
Birmingham Hyatt House
901 North 21st Street
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The Department of Continuing Education in Health Sciences and The Jules Stein Eye Institute, UCLA
Announces A One-Day Seminar

Current Concepts in Ophthalmic Plastic Surgery: "The Eye Lid"

Saturday, November 15, 1975
Neuropsychiatric Institute
Auditorium, UCLA

Guest Faculty: Drs. C. Beard, R. Dryden, J. Langham, C. Leone, C. McCord, R. Tenzel, and R. Wilkins

UCLA Faculty: Drs. H. Baylis, R. Hepler, D. Kamin, T. Pettit, B. Straatsma, H. Zarem

For detailed information, contact the Dept. of Continuing Education in Health Sciences, UCLA Extension, Los Angeles, CA 90024 or telephone Sue Oliver (213) 825-7257.

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Morning LECTURES — Classification, Diagnosis, and Fluorescein Angiography

Afternoon WORKSHOPS — Management, Treatment, Reading of Stereo Angiograms

FRIDAY and SATURDAY, OCTOBER 31 — NOVEMBER 1, 1975

Emanuel Rosen	*England*	Chris Zweng	*Palo Alto*
Hunter Little	*Palo Alto*	Kurt Gitter	*New Orleans*
Steve Ryan	*Los Angeles*	Maurice Rabb	*Chicago*
Lawrence Yannuzzi	*New York*	Tom Burton	*Iowa City*
John Justice	*Houston*	Howard Schatz	*San Francisco*
J. Brooks Crawford	*San Francisco*	(Course Director)	

Fee: $135.00 ($145.00 at the door), Residents and Technicians $60.00

To be held at the Hyatt on Union Square, Downtown San Francisco. Fee includes luncheons & reception.

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3637 Sacramento, San Francisco, 94118
or call: (415) 921-4860

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Enrollment limited to 20 Fee: $1,000.00

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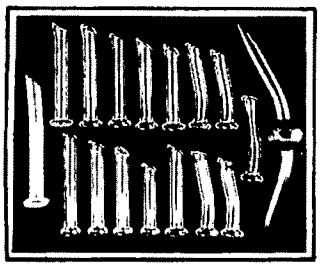
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*L. T. JONES, M.D. DACRYOCYSTORHINOSTOMY, AMERICAN JOURNAL OF OPHTHALMOLOGY, VOLUME 59, NO. 5, MAY 1965.

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Announcement of the

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March 4-5-6, 1976

Sponsored by THE RUDOLPH ELLENDER MEDICAL FOUNDATION

A.M.A.—approved as continuing medical education program (Twenty Hours Credit in Category I)

PLACE:	Fairmont-Roosevelt Hotel, New Orleans
TUITION:	$175.00 ($75.00 Ophthalmology Residents)
FACULTY:	JAMES V. AQUAVELLA, M.D., Rochester, New York JOS. A. BALDONE, M.D., New Orleans PERRY S. BINDER, M.D., San Diego, California OLIVER H. DABEZIES, JR., M.D., New Orleans JACK HARTSTEIN, M.D., St. Louis, Missouri FRANK B. HOEFLE, M.D., New York City PAUL R. HONAN, M.D., Lebanon, Indiana HAROLD P. KOLLER, M.D., Cherry Hill, New Jersey WHITNEY G. SAMPSON, M.D., Houston, Texas
SPECIAL GUEST LECTURER:	HERBERT E. KAUFMAN, M.D., Gainesville, Florida Saturday, March 6, 1976—Corneal Surgical Techniques at Cataract Surgery to Facilitate Contact Lens Fitting
TOPICS:	Conventional hard contact lenses, hydrophilic soft gel lenses, silicone lenses, oxygen permeable hard contact lenses, aspheric, variable focus lenses, and intraocular lens implants.
PRE-MEETING COURSES: Wed., Mar. 3rd p.m.	Basic Lectures—by Industry—No additional fee.
LADIES DAY:	Activities Planned (Usually French Quarter & Garden District Tours)
	COME EARLY FOR THE MARDI GRAS SEASON, Feb. 28, March 1-2, 1976 Mardi Gras Day is Tuesday, March 2, 1976 Special convention hotel rates for Mardi Gras (to a limited number of registrants) Or you may avoid Mardi Gras by arriving New Orleans Wed. March 3rd
POST-COURSE	Gulf of Mexico Cruise out of the Port of New Orleans Call or write: George Scherer—Rownd Scherer Travel Service P.O. Box 368 Hammond, La. 70401 Ph: 504-345-4048
For further information contact:	Jos. A. Baldone, M.D. Roof, Delta Towers—Canal at Claiborne New Orleans 70112 USA Ph: 504-524-9729

1976 COURSE IS DEDICATED TO THE MEMORY OF THE LATE WM. BURTON CLARK, M.D.

THE UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

Department of Ophthalmology and the

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present a dedication symposium on

CURRENT CONCEPTS IN OPHTHALMOLOGY

December 2-3, 1975

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The Wilmer Ophthalmological Institute
Baltimore, Maryland

Arthur Jampolsky, M.D.
Smith-Kettlewell Institute of Visual Sciences
San Francisco, California

A. Edward Maumenee, M.D.
The Wilmer Ophthalmological Institute
Baltimore, Maryland

Edward W. D. Norton, M.D.
Boscom Palmer Eye Institute
Miami, Florida

LECTURERS

David Paton, M.D.
Baylor University
Houston, Texas

Lorenz Zimmerman, M.D.
Armed Forces Institute of Pathology
Washington, D.C.

Bradley Straatsma, M.D.
The Jules Stein Eye Institute
Los Angeles, California

Frank B. Walsh, M.D.
The Wilmer Ophthalmological Institute
Baltimore, Maryland

LECTURES AND PANEL DISCUSSIONS TO INCLUDE:

The Cornea
Neuro ophthalmology
Practical plastic procedures
Current and future ophthalmic research

LECTURES AND PANEL DISCUSSIONS TO INCLUDE:

Anterior segment surgery
Phacoemulsification
Intra ocular lenses
Strabismus
Glaucoma

for further information contact:

Caroline Cannon
Dean A. McGee Eye Institute
800 N.E. 15th Suite 421
Oklahoma City, Oklahoma 73104

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**2nd ANNUAL
ROCKY MOUNTAIN
NEURO-OPHTHALMOLOGY
COURSE**

SANTA FE HILTON INN
Santa Fe, New Mexico
February 5, 6, 7, 1976

FACULTY

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This course will include lectures and seminar sessions covering basic disorders of ocular motility and the visual system. Ample time between sessions has been provided for leisure activity in Santa Fe and the nearby ski area.

Tuition: $175.00 provides transportation by chartered bus between hotel and ski facilities, one breakfast and evening banquet.

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The Retina Service of Wills Eye Hospital
and
Jefferson Medical College of Thomas Jefferson University
announce a comprehensive course on
March 6 and 7, 1976

VASCULAR DISEASES OF THE OCULAR FUNDUS

Faculty:
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Paul Carmichael, M.D.
Thomas Duane, M.D.
Jay L. Federman, M.D.
Richard E. Goldberg, M.D.
Alfred Lucier, M.D.
Larry Magargal, M.D.
P. Robb McDonald, M.D.
Peter Palena, M.D.
Charles C. Rife, M.D.
Lov K. Sarin, M.D.
Norman J. Schatz, M.D.
Jerry A. Shields, M.D.
George L. Spaeth, M.D.
William Tasman, M.D.
Peter Walsh, M.D., Ph.D.
Albert Zimmermann, M.D.

Guest Lecturer—Paul Henkind, M.D., Ph.D.

Location: Jefferson Hall Commons, Philadelphia, Pa.
Tuition: $175.00. Special rate of $60.00 for residents and fellows.
Make checks payable to Retina Service, Wills Eye Hospital, and mail to Retina Service, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pa. 19130. Fee includes luncheons and Dinner.*

For programs, hotel reservations, wives' Bicentennial activities, write to:
Richard E. Goldberg, M.D.
Retina Service, Wills Eye Hospital
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Philadelphia, Pa. 19130

Good for Accreditation in Category 1

*Wills Eye Ex-Retina Fellows Alumni Dinner—Friday night, March 5, 1976

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A POSTGRADUATE COURSE

CLINICAL APPLICATIONS of VITREOUS SURGERY

Thursday and Friday • February 12 and 13, 1976

This course will stress pre and post op management as well as indications for surgery. Special emphasis will be placed on the use of vitrectomy in diabetes, trauma, retinal detachments and anterior segment disease.

Guest Faculty:

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ROBERT MACHEMER, M.D.
RONALD G. MICHELS, M.D.
A. WALLACE McMEEL, M.D.

USC Faculty:

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*Registration fee: **$195.00** **Resident's fee: **$25.00**

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FORTY-NINTH ANNUAL NEW YORK EYE AND EAR INFIRMARY CLINICAL CONFERENCE

MAY 12-13, 1976

SURGICAL JUDGEMENT IN OPHTHALMOLOGY— "WHAT TO DO AND WHEN TO DO IT"

IN

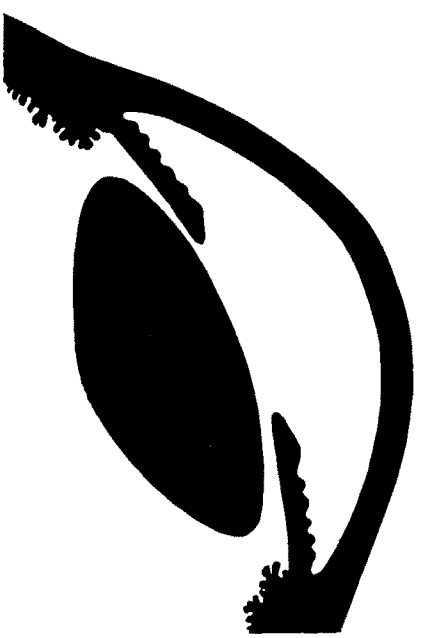
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AND

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ADVANCED SPRING CONTACT LENS SEMINAR
MAY 14, 1976

For further information, please write:
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Diseases and Surgery of the Anterior Segment
November 13-15, 1975



The Wilmer Ophthalmological Institute
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Guest Faculty:
Dan B. Jones, M.D.
Ronald E. Smith, M.D.

Wilmer Faculty:
A. Edward Maumenee, M.D.
W. Richard Green, M.D.
W. Jackson Iliff, M.D.
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Credit:
18 hours Category I, American Medical Association

Registration Fee:
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For Information, Contact: Walter J. Stark, M.D.
Course Director
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UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

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MIAMI BEACH, FLORIDA

DECEMBER 7-10, 1975

AMERICANA HOTEL
MIAMI BEACH, FLORIDA

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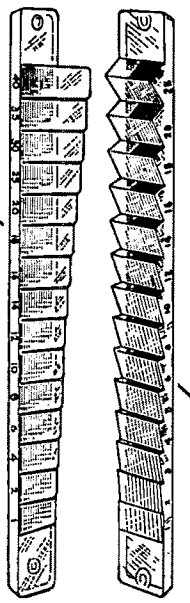
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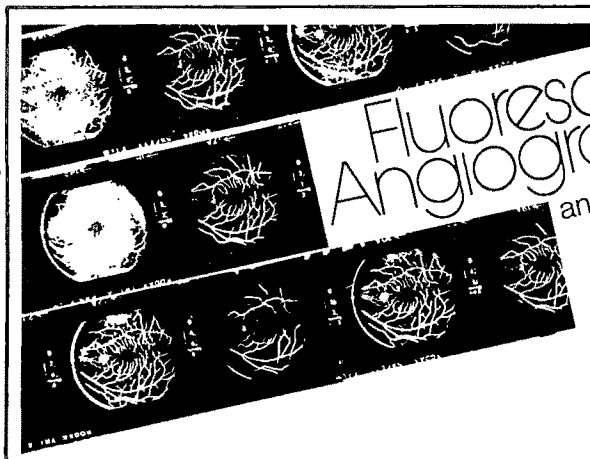
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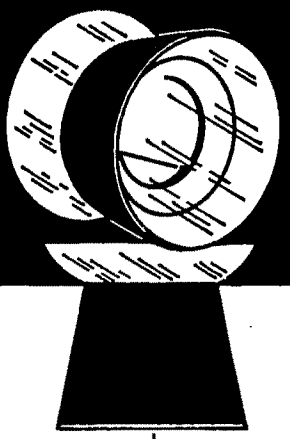
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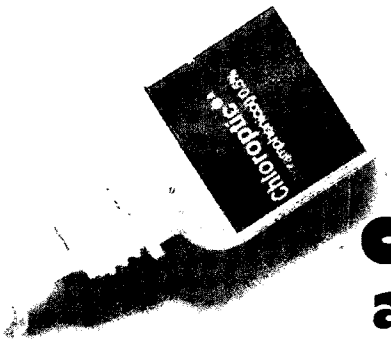
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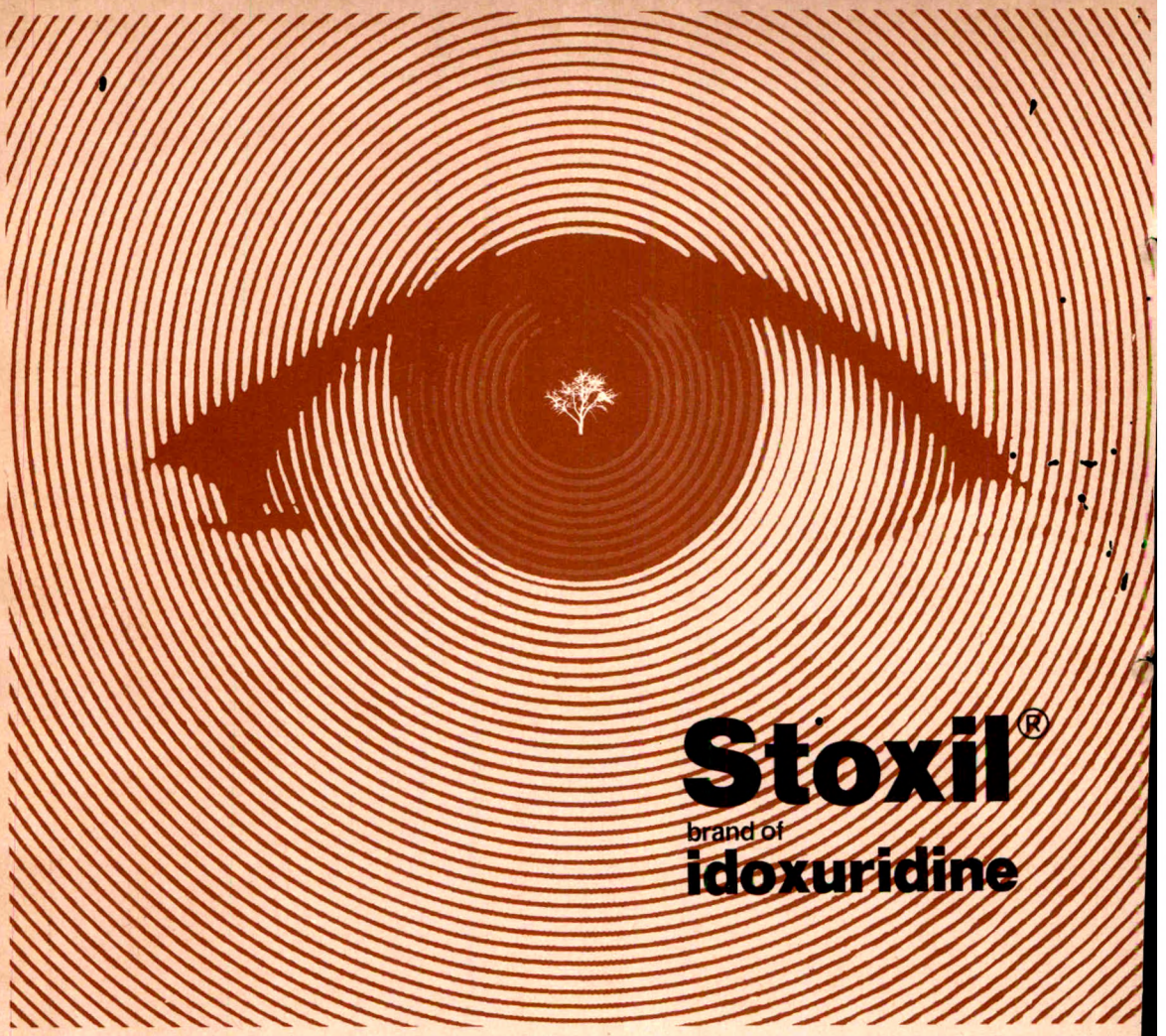
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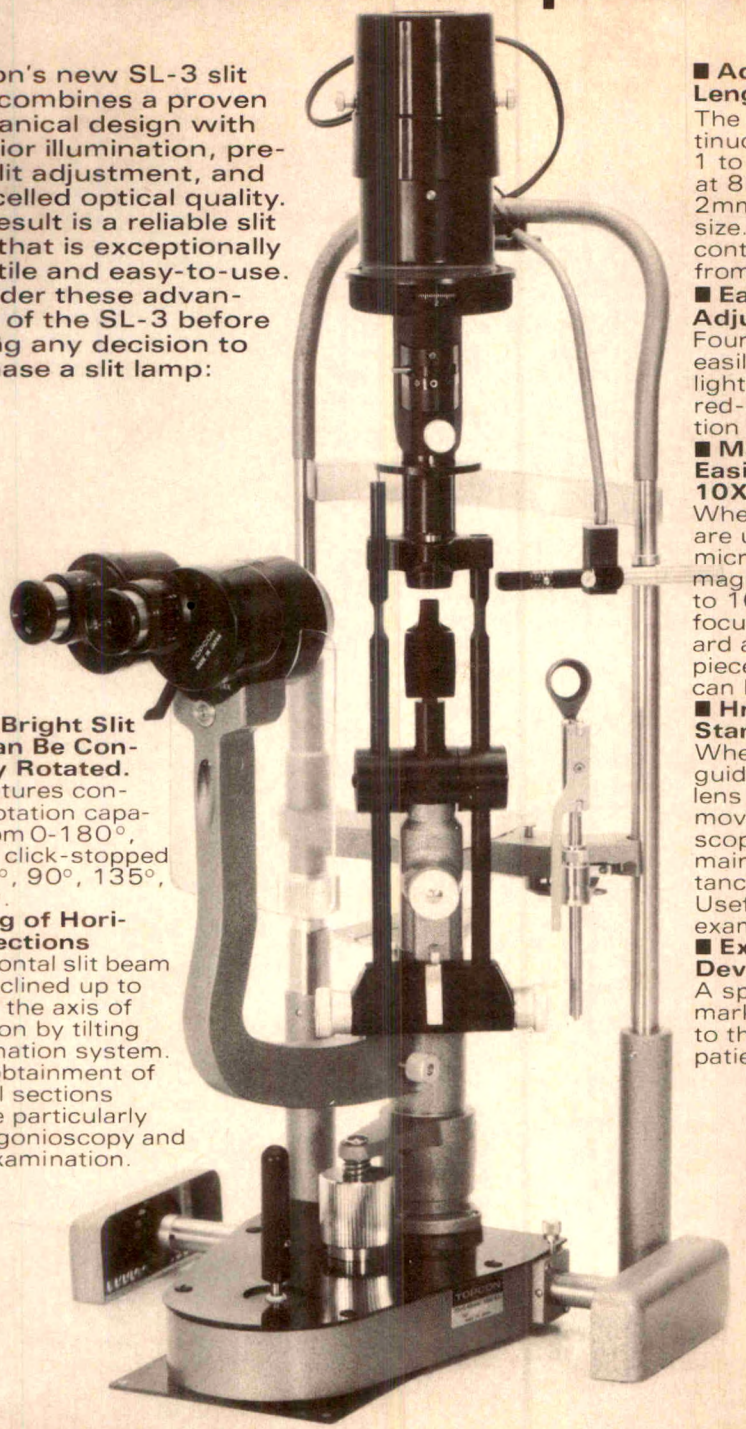
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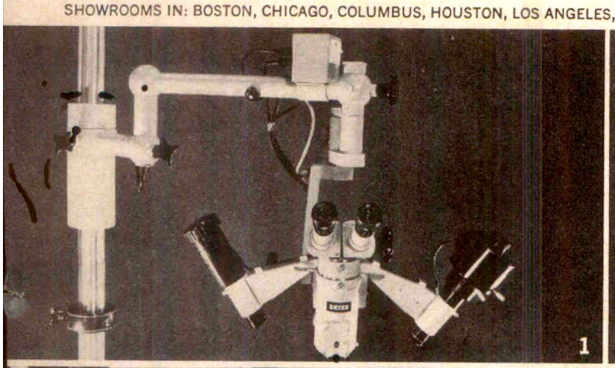
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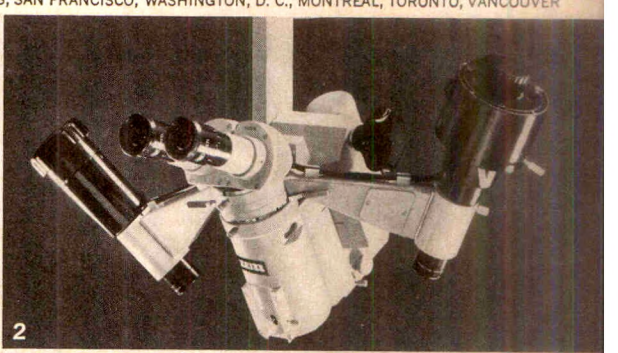
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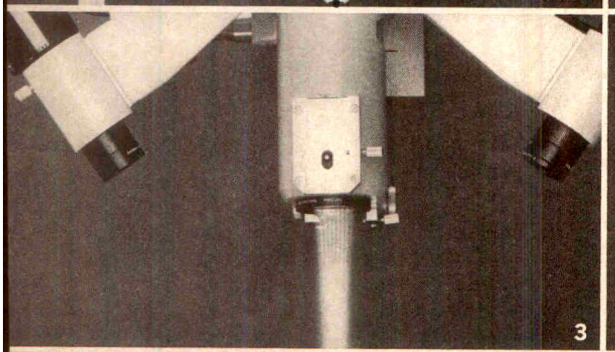
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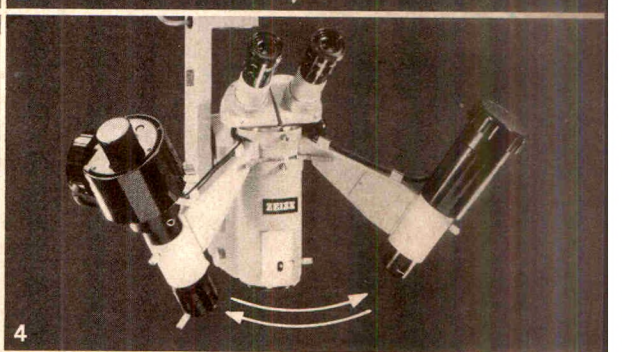
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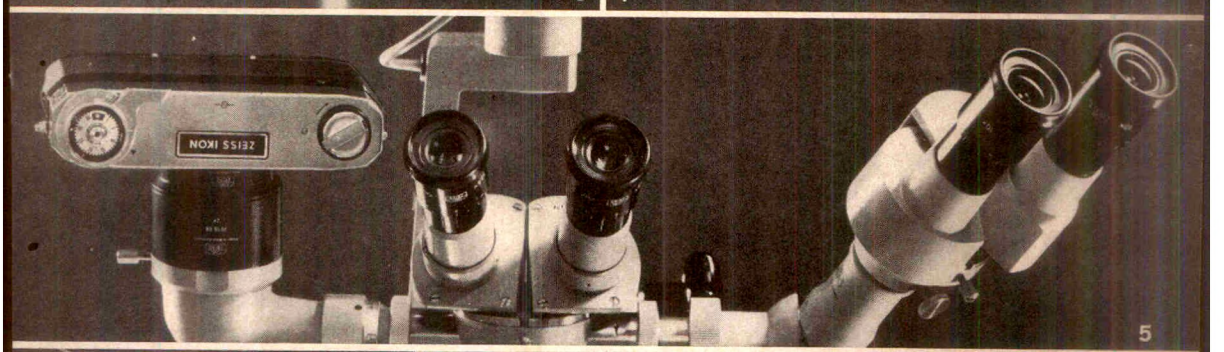
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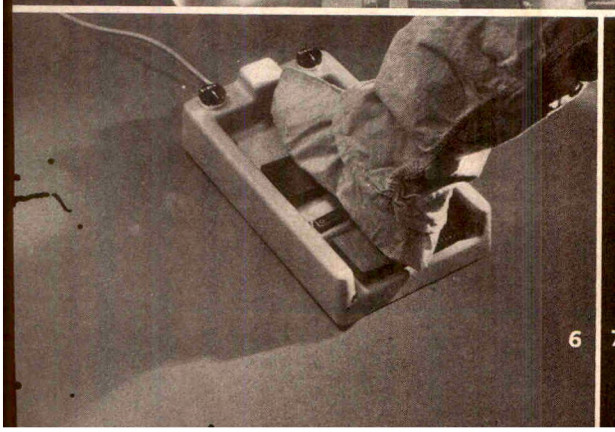

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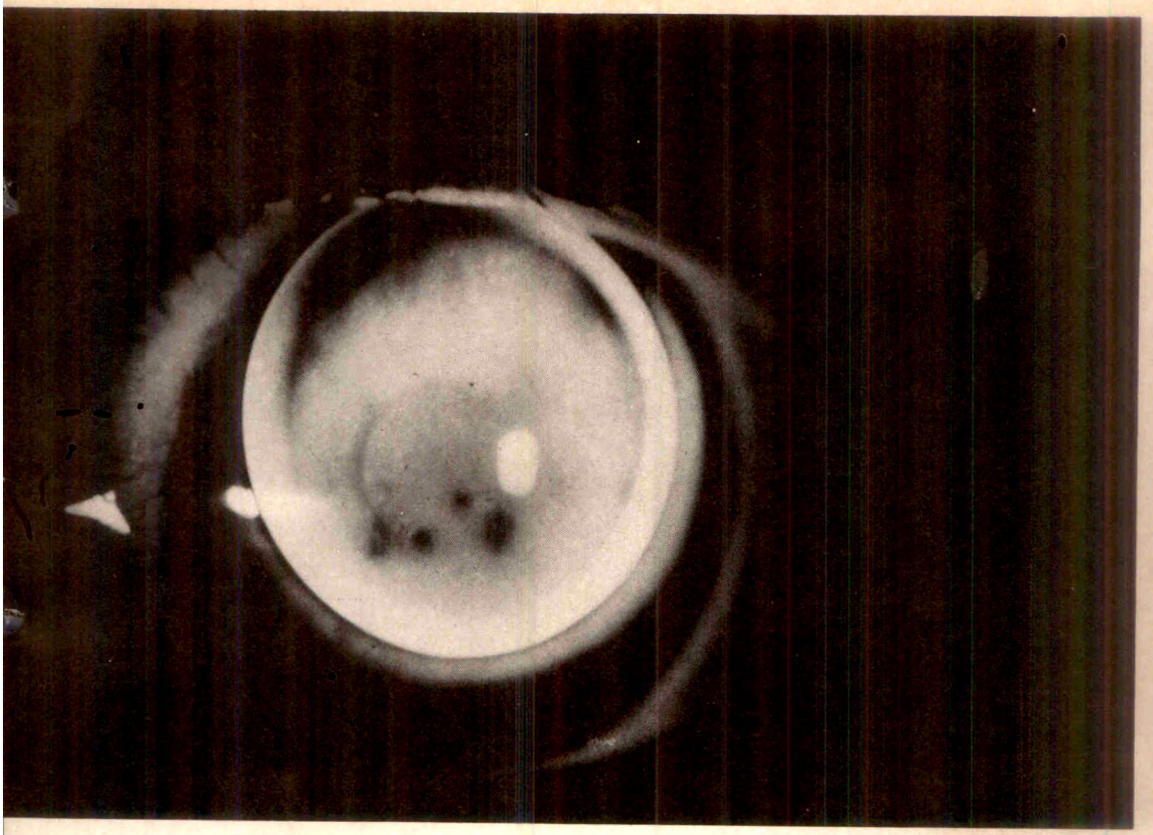
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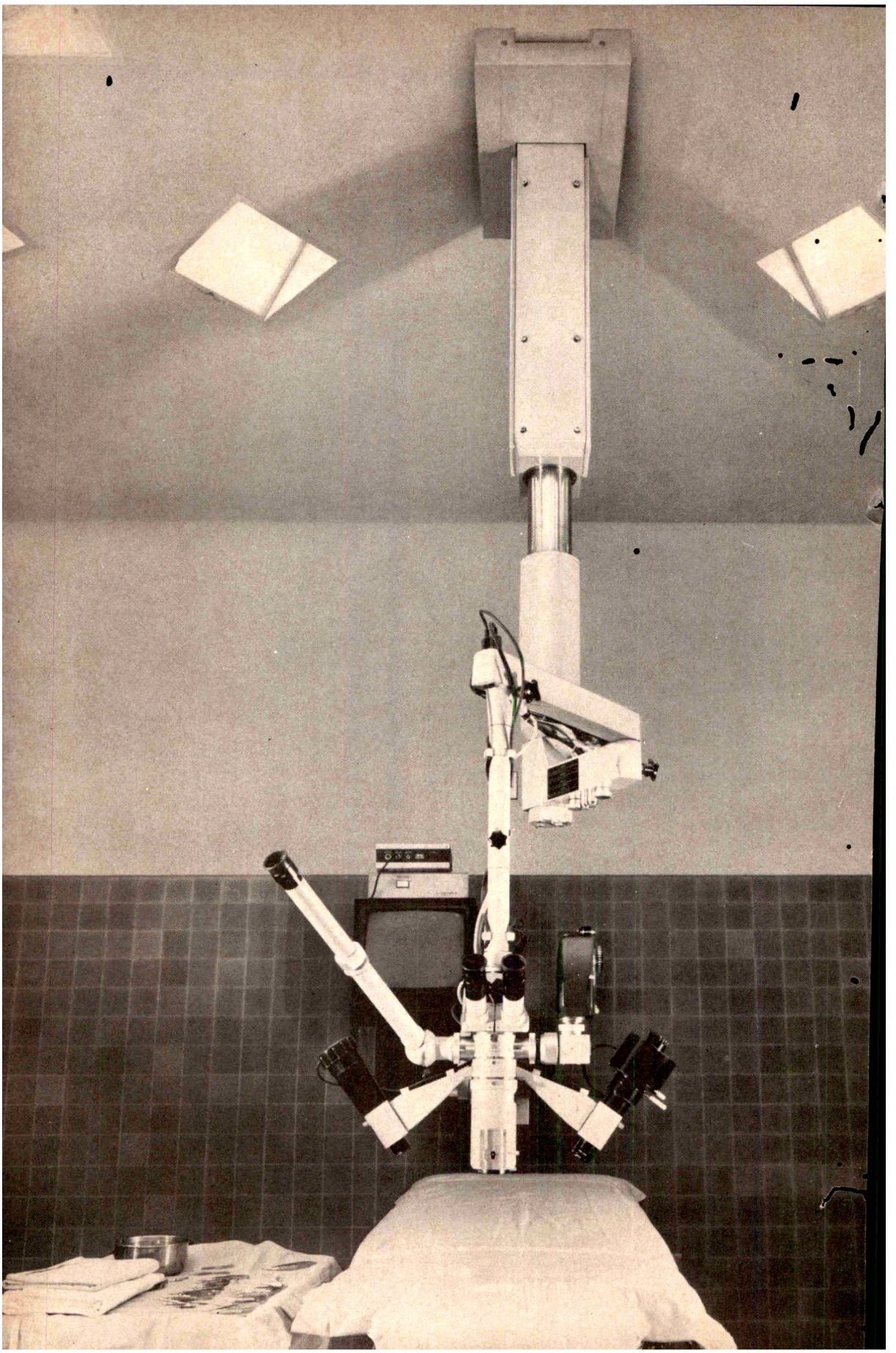
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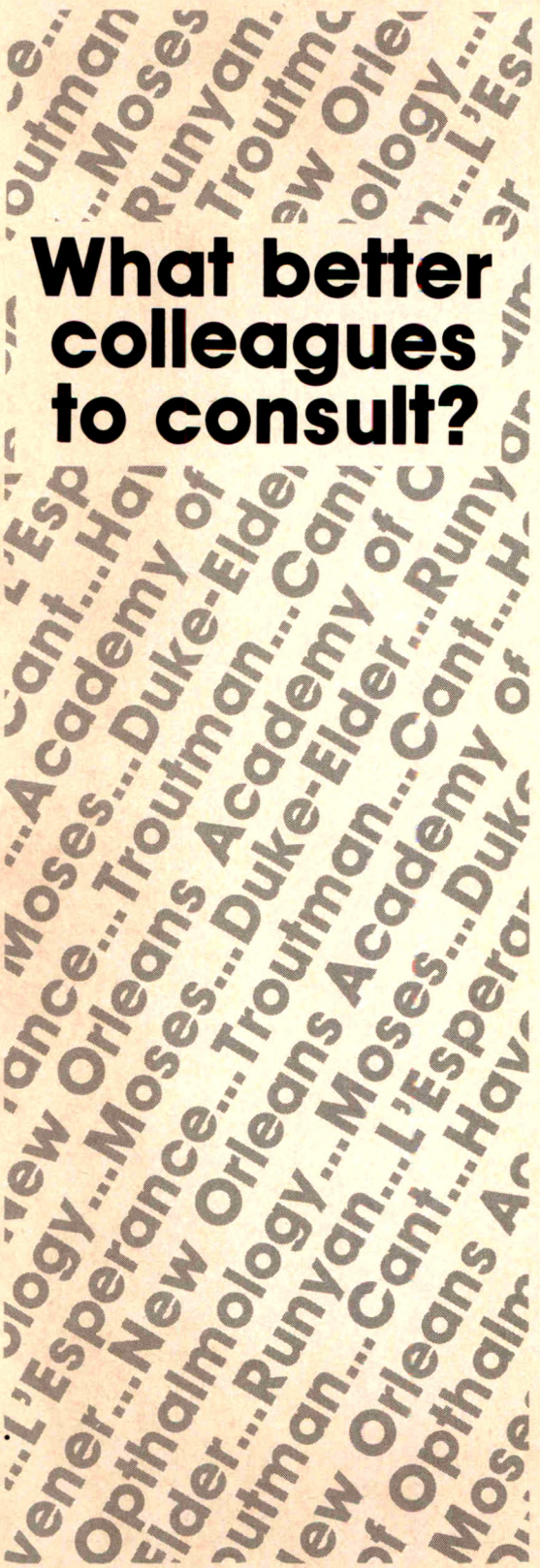
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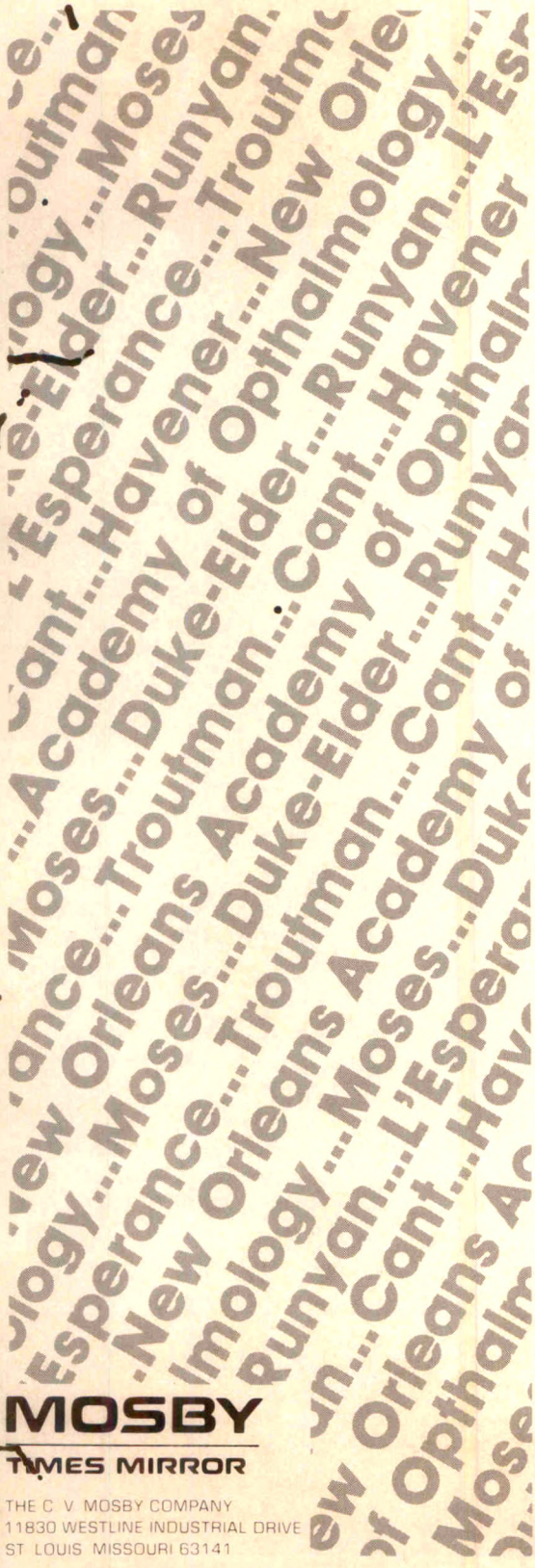
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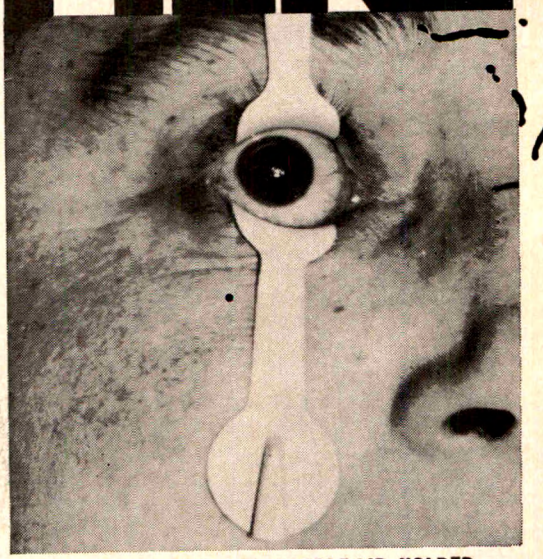
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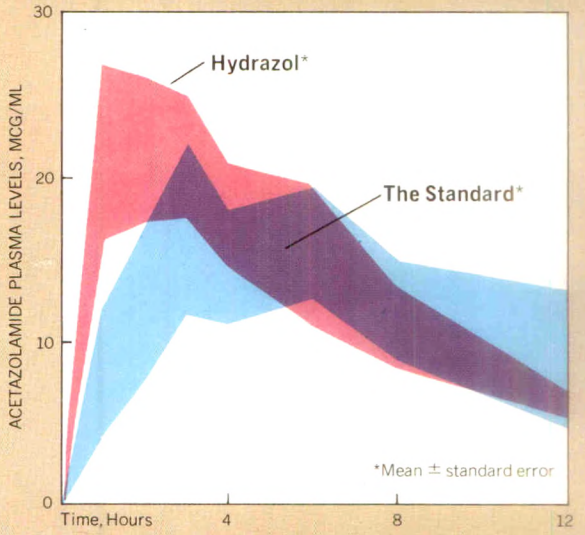
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During long-term therapy, an acidotic state may occasionally supervene. This can usually be corrected by the administration of bicarbonate.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuance of the medication.

Other occasional adverse reactions include: urticaria melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, and convulsions.

Dosage and administration: Hydrazol (acetazolamide) should be used as an adjunct to the usual therapy for glaucoma. The dosage employed in the treatment of *chronic simple (open-angle) glaucoma* ranges from 250 mg to 1 gram of acetazolamide per 24 hours, usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 1 gram per 24 hours does not produce an increased effect. In all cases, the dosage should be adjusted with careful individual attention both to symptomatology and ocular tension. Continuous supervision by a physician is advisable.

In the treatment of secondary glaucoma and in the preoperative treatment of some cases of *acute congestive (closed-angle) glaucoma*, the preferred dosage is 250 mg every four hours, although some cases have responded to 250 mg twice daily on short-term therapy. In some acute cases, it may be more satisfactory to administer an initial dose of 500 mg followed by 125 or 250 mg every 4 hours, depending on the individual case. A complementary effect has been noted when acetazolamide has been used in conjunction with miotics and mydriatics as the case demanded.

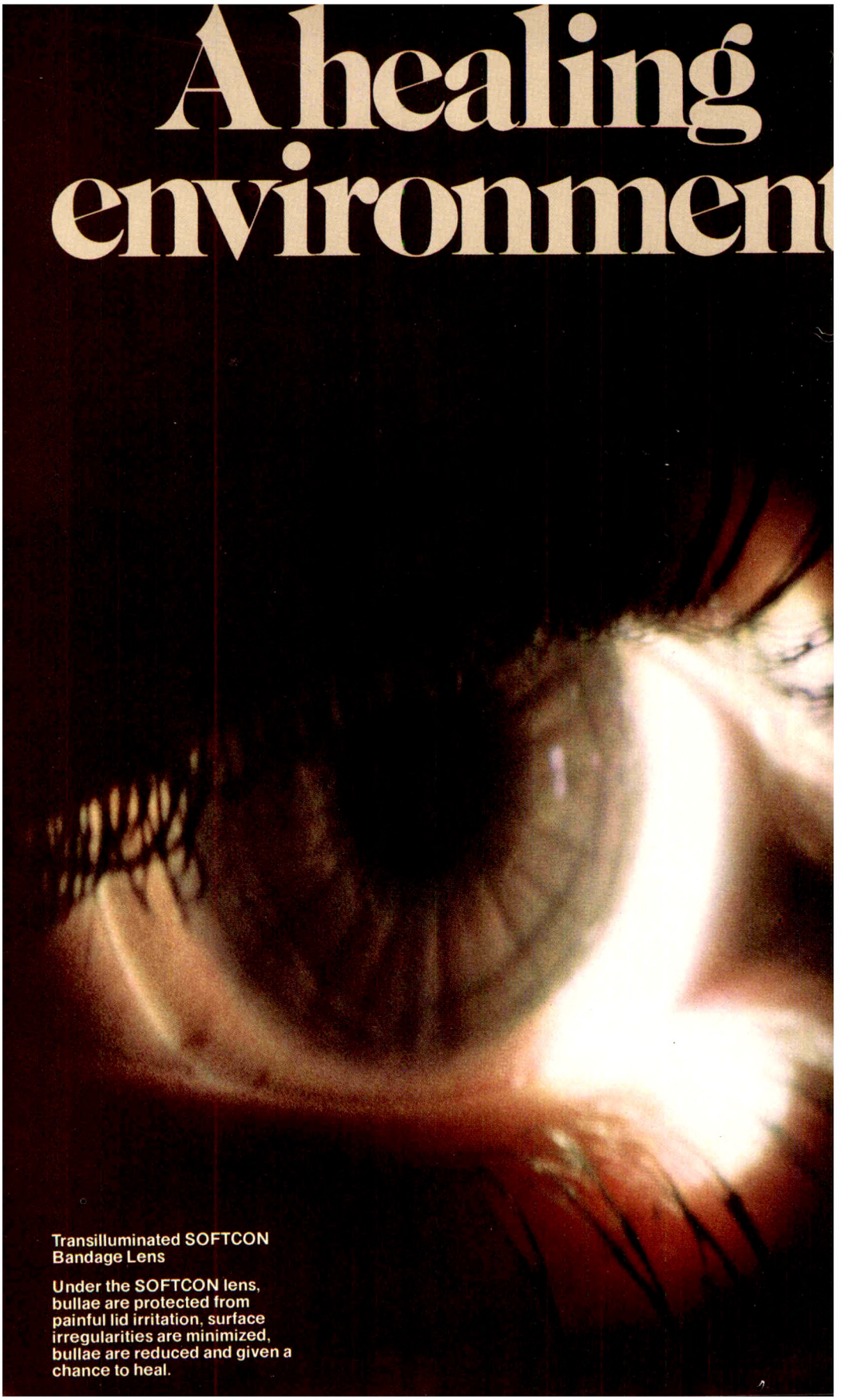
Note: The dosage recommendations for glaucoma differ considerably from those for other indications for acetazolamide, since treatment of glaucoma is not dependent upon carbonic anhydrase in the kidney.

How supplied: 250 mg round, yellow, quarter-scored tablets; coded "SP 250." (NDC 0346-0250-51) bottles of 100.

Full information is available on request.

Softcon Products
Div. Warner-Lambert Company
Morris Plains, N.J. 07950

A healing environment



Transilluminated SOFTCON Bandage Lens

Under the SOFTCON lens, bullae are protected from painful lid irritation, surface irregularities are minimized, bullae are reduced and given a chance to heal.

Softcon®
(vifilcon A)
BANDAGE LENS
for the treatment of bullous keratopathy

A protective cover that can bring immediate and complete relief of pain

Until now, the pain of bullous keratopathy was often a virtual mandate for surgery. Now the SOFTCON Bandage Lens offers the patient round-the-clock pain relief and the physician a welcome opportunity to watch and wait. Edema may be so well controlled with the SOFTCON lens and hypertonic saline, that other measures never become necessary. In any case, an interim period of SOFTCON lens wear won't compromise future alternatives. In a study of 419 eyes with bullous keratopathy, the SOFTCON lens gave complete pain relief in 74% of cases and partial relief in 20%[1]

Distinct physical properties that enhance corneal metabolism

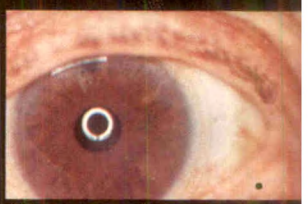
The SOFTCON lens is gel-like and virtually nonirritating, yet holds the curvature necessary for optical stability. The hydrophylic SOFTCON lens is about 55% water, equilibrates with the tear layer, and is permeable to oxygen and carbon dioxide. In a study of 465 eyes with bullous keratopathy, corneal status improved (by slit lamp evaluation) during SOFTCON lens wear in 66%, was unchanged in 30%, and worsened in only 3%[1]

A chance to preserve and even improve visual acuity during therapy

Before SOFTCON, treatment for severe corneal edema usually meant loss or limitation of existing visual acuity. A study of SOFTCON lens wear in 364 eyes with bullous keratopathy showed that visual acuity *improved significantly* in 33%, remained unchanged in 63%, and declined in only 4%[1]



Aphakic Fuchs' dystrophy. Note irregular reflex although cornea appears grossly clear. Acuity 20/160.



After almost 2 years of continuous SOFTCON bandage lens wear. 5% hypertonic saline solution b.i.d. Acuity 20/25 with overspectacles.

Softcon® (vifilcon A)

BANDAGE LENS

for bullous keratopathy



DESCRIPTION The SOFTCON (vifilcon A) corneal bandage lens is a semispherical flexible shell which covers the cornea and the adjacent sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, N.F. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON bandage lens may be useful in the treatment of bullous keratopathy to aid corneal healing, to relieve pain, to reduce corneal edema and, in selected cases, to improve vision.

CONTRAINDICATIONS Presence of any active infection of the eye.

WARNINGS The SOFTCON (vifilcon A) lens must be stored aseptically only in Lensrins™ NP. Use of other solutions, drops or cleaners may result in irritation or injury to the eye.

Patients must be instructed to consult their physician immediately if the eye becomes uncomfortable or irritated.

The lens must not be used in combination with solutions commonly used for cleansing, wetting and storage of conventional hard acrylic contact lenses, or with over-the-counter eye drops or medications. These solutions or medications may cause serious damage to the cornea when used with the corneal bandage lens. Cosmetics and hair sprays must not be allowed to come in contact with the lens. Patients should be warned accordingly. Safety in pregnancy has not been substantiated.

PRECAUTIONS Active eye infections should be appropriately treated before the insertion of the SOFTCON (vifilcon A) bandage lens.

Medications necessary to treat the disease condition should be used with caution, under close supervision. Hypertonic saline drops have been used concurrently without adverse effects. Quaternary ammonium compounds and other preservatives may cause ocular irritation. Other agents, epinephrine and fluorescein, for example, will cause discoloration of the lens.

Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Rarely a lens may adhere to an eye as a result of wearing a hypotonic lens. If a lens adheres for any reason, apply Lensrins NP and wait until the lens moves freely before removing it.

Lenses exposed to the air will dehydrate and become brittle. If this occurs, the lens should be soaked in Lensrins NP for one hour.

ADVERSE REACTIONS The following adverse reactions have been reported in patients using this lens for bullous keratopathy: corneal ulcer, ocular inflammation, ocular pain, hyperemia, keratoconjunctivitis, candida keratitis, neovascularization, excessive tearing and conjunctival injection.

Pain relief and improved corneal status in most patients; untoward experiences in very few

IN A STUDY OF 493 EYES (461 PATIENTS) WITH BULLOUS KERATOPATHY[1]:

Final wearing status

Lens wear continued	65%
Lens therapy completed	23%
Lens wear terminated	9%
Not stated	3%

Untoward experience during lens therapy

No	72%	Yes	28%

Type of untoward experience

Lost	24
Torn	18
Discolored	14
Uncomfortable	46
Deposit on lens	24
Not stated	5

DOSAGE AND ADMINISTRATION

Cleaning and Disinfecting Procedures

If the lens requires cleaning, it should be removed and cleaned by the physician by gently rubbing both sides of the lens between the fingers with a drop or two of Lensrins NP, followed by a rinse with lukewarm Lensrins NP. Any lens removed from the eye should be disinfected before being reapplied to the eye. The lens should be transferred to the glass vial supplied, filled three-quarters full with Lensrins NP and stoppered with a silicone rubber stopper. The vial is then closed with an aluminum tear seal, crimped with a crimping tool and then boiled for at least fifteen minutes in either a boiling water bath or office sterilizer. Allow the lens to cool before removing from the vial and insertion onto the eye.

Insertion and Removal Lenses should be applied and removed only by the physician. All patients should be instructed in the technique of removing a lens should this become necessary.

Fitting and Wearing Schedule Patients may be fitted with lenses in refracting powers ranging from high minus (−25.00 D) to high plus (+25.00 D) in 0.50 diopter steps. These lenses are not recommended for use in cases of ametropia to correct visual acuity.

The SOFTCON (vifilcon A) bandage lens is to be worn continuously, for 24 hours a day, following initial application. Patients should be followed closely during initial stages of treatment. The lens should be comfortable and the pain of bullous keratopathy should be relieved. If the lens is not comfortable and pain persists, another lens should be tried for appropriate fit.

Patients should be examined periodically for proper fit of the lens. A healing cornea may change in geometric relationship between the eye and the lens. Intolerance and discomfort experienced during healing can usually be eliminated by refitting the eye with a different lens. It is not ordinarily necessary to remove the lens from the patient's eye at each follow-up visit. The lens can be examined on the eye with a slit lamp.

HOW SUPPLIED Each SOFTCON (vifilcon A) lens is supplied sterile in a glass vial containing sodium chloride solution, USP. The label shows base curve, diameter, refractive power in diopters and thickness.

The following are the common lens dimensions available:

Base Curves (mm of radius)	7.8	Overall Chord Diameters (mm)	13.5
	8.1		14.0
	8.4		14.5
	8.7		15.0

For lens cleaning or disinfecting, the following materials are available:

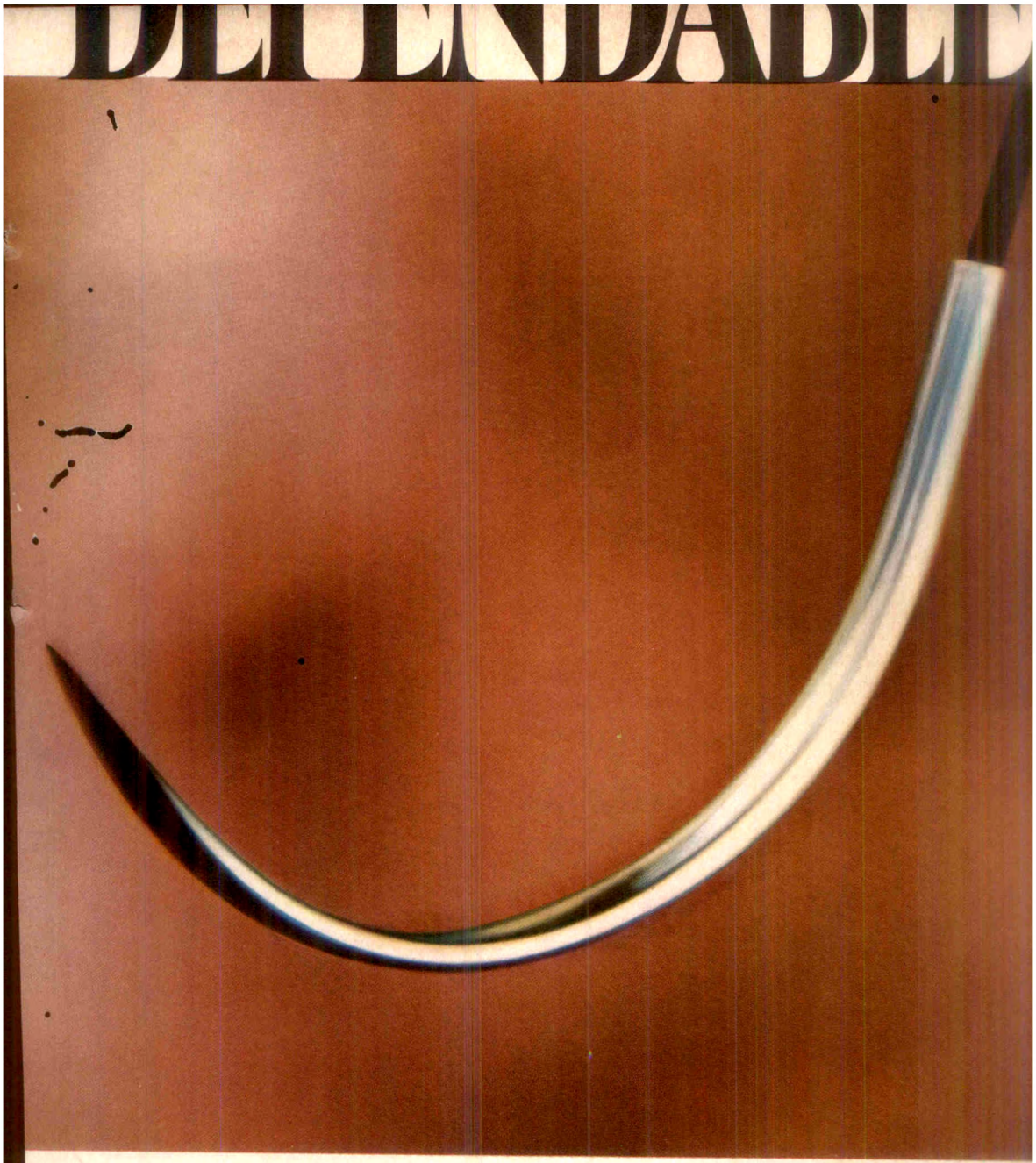
Lensrins NP; type I glass vials, 5 cc.; silicone rubber stoppers; aluminum seals; crimping tool (available directly from the West Co., Phoenixville, Penna 19460—Fermpress H 207).

CAUTION: Federal Law Prohibits Dispensing Without A Prescription.

Reference: 1. Data on file, Softcon Products, Div., Warner-Lambert Co.

Softcon Products
Div., Warner-Lambert Company
Morris Plains, N.J. 07950

For further information on any items in the Softcon Products line, write to Softcon Products Professional Services Dept., 201 Tabor Road, Morris Plains, New Jersey 07950.



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Registrants will be instructed in the indications and various methods of lens implantation by European and American pioneers in the technique. Complications will be discussed by experts in the various sub-specialties of ophthalmology. Information will be provided on federal regulations, informed consent and the sources of the various lens types commercially available.

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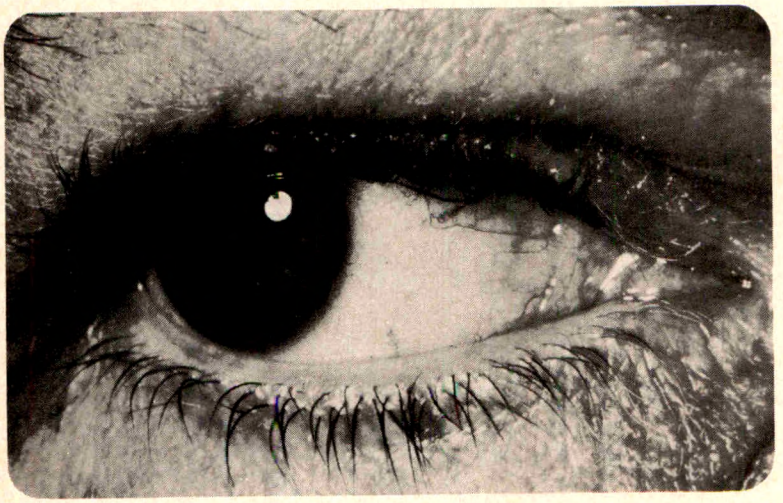
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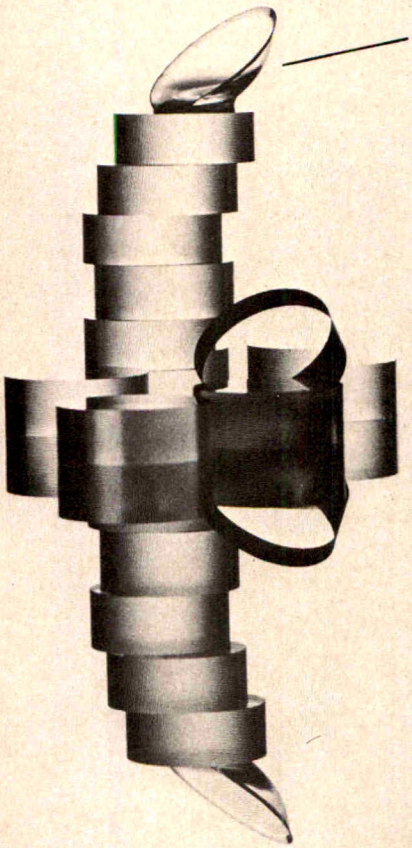
Yet this selection offers you a wide range of base curves and diameters. Enough to satisfy the majority of fitting problems in the correction of ametropia.

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The lathe-cut, soft, hydrophilic contact lens, now available from Soft Lenses, Inc.

The versatile one

HYDROCURVE™

(hefilcon A)

Contact Lens PHP*

From Soft Lenses, Inc.
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8006 Engineer Rd., San Diego, CA 92111

HydroCurve™ Soft Lenses, Inc. *PHP (U.S. Pat. 3,721,657) Trade Mark of Automated Optics, In

HYDROCURVE™ (hefilcon A) CONTACT LENS

fabricated from PHP* polymer (poly (2-hydroxyethyl methacrylate) 46% Water 54%)

DESCRIPTION—The HydroCurve® (hefilcon A) Contact Lens PHP* is a hemispherical shell of approximately 14 mm. chord diameter and 0.1 to 1.0 mm. thickness. It consists of 46% poly (2-hydroxyethyl methacrylate) and 54% water by weight when immersed in normal saline.

ACTIONS—In its hydrated state a HydroCurve® (hefilcon A) Contact Lens PHP* becomes soft and pliable. When placed on the human cornea the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43.

INDICATIONS—HydroCurve® (hefilcon A) Contact Lenses PHP* are indicated for the correction of visual acuity in persons with nondiseased eyes who have spherical ametropias; refractive astigmatism of 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS—HydroCurve® (hefilcon A) Contact Lenses PHP* are contraindicated by the presence of any of the following conditions:

1. Acute and subacute inflammations of the anterior segment of the eye.
2. Any eye disease which affects the cornea or conjunctiva.
3. Insufficiency of lacrimal secretion.
4. Corneal hypoesthesia.
5. Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Medicants and Eye Drops: The HydroCurve® (hefilcon A) Contact Lens PHP* must be stored ONLY in BOILnSOAK® Solution. No ophthalmic solutions or medicants, including conventional contact lens solutions, can be used by HydroCurve® (hefilcon A) Contact Lens PHP* wearers prior to or while the lens is in place on the eye. Also, no solutions, including conventional contact lens solutions, other than BOILnSOAK® and the recommended cleaners BOILnSOAK® or Pliagel® or Soft/Mate® may be used on the HydroCurve® (hefilcon A) Contact Lens PHP* when the lens is off the eye.

Abrasions and Infections: If the lenses become less comfortable to the wearer than when they were first placed on the wearer's corneas, this may indicate the presence of a foreign body. The lens should be removed immediately and the patient examined. If any eye abrasion, ulceration, irritation or infection is present, a physician should be consulted immediately.

Lens Sanitation: Patients must adhere to recommended daily sanitary care of the HydroCurve® (hefilcon A) Contact Lenses PHP*. Failure to follow this procedure may result in development of serious ocular infections.

Wearing Restrictions: The HydroCurve® (hefilcon A) Contact Lens PHP* should be removed before sleeping or swimming or in the presence of noxious and irritating vapors.

Visual Blurring: When visual blurring occurs the lens must be removed until the condition subsides.

PRECAUTIONS

Storage: HydroCurve® (hefilcon A) Contact Lenses PHP* must be stored ONLY in BOILnSOAK® Solution. If left exposed to air, the lenses will dehydrate. If a lens dehydrates, it should be soaked in BOILnSOAK® Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: HydroCurve® (hefilcon A) Contact Lenses PHP* must be BOTH cleaned and disinfected daily. One procedure does not replace the other. CLEANING is necessary to remove mucus and film from the lens surface. This can be accomplished by using either BOILnSOAK® or Pliagel® or Soft/Mate® on a daily basis. Excessive deposits may damage the lens; therefore, if this occurs, review care of lens with patient.

DISINFECTING with the Hydrotherm® Patient Unit and BOILnSOAK® Solution has been shown to prevent the growth of certain organisms, namely Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Herpes simplex, on the lens and in the HydroCurve® Carrying Case with the porta-FLOW® Transfer Unit (basket).

HydroCurve® (hefilcon A) Contact Lenses PHP* must be cleaned daily with fresh BOILnSOAK® Pliagel® or Soft/Mate.® Fresh BOILnSOAK® Solution must be used only for storing the lenses. The HydroCurve® Carrying Case must be emptied and refilled with fresh BOILnSOAK® Solution just before disinfecting the lenses.

If a Hydrotherm® Patient Unit is not available for disinfecting the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.

Hygiene: Patients must be instructed to wash and rinse hands thoroughly, and dry with a lint-free towel before handling the lenses.

Cosmetics, lotions, soaps and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS—Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, patients may be instructed to apply a few drops of BOILnSOAK® Solution and wait until the lens moves freely before removing it.

Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms.

Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION—Conventional methods of fitting contact lenses do not apply to HydroCurve® (hefilcon A) Contact Lenses PHP*. For a detailed description of the fitting technique, refer to the HydroCurve® Fitting Guide, additional copies of which are available from: Soft Lenses, Inc., 8006 Engineer Road, San Diego, California 92111.

There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

Day	Maximum Wearing Time (Continuous Hours)	Day	Maximum Wearing Time (Continuous Hours)
1	3	8	8
2	3	9	8
3	4	10	10
4	4	11	12
5	6	12	14
6	6	13	15
7	8	14	all waking hours*

*Lenses should never be worn 24 hours a day.

Care must be taken on the initial visit to assure that the patient is supplied with a HydroCurve® Patient Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.



In Use Durability: With normal use and patient care, HydroCurve® (hefilcon A) Contact Lenses PHP* have been shown to be durable for a minimum of one year.

HOW SUPPLIED—Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the base curve, dioptric power, diameter, thickness and the manufacturing lot number of the lens.

To assure proper lens care and handling, each HydroCurve® patient must be supplied with a complete HydroCurve® Patient Care Kit.

The HydroCurve® Patient Care Kit is a package required for lens cleaning, disinfecting and storing consisting of the following:

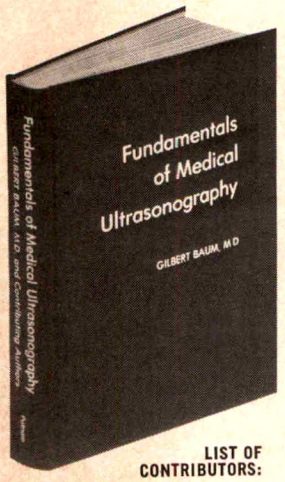
porta-FLOW® Transfer Unit (basket)	Cat. # 1001
HydroCurve® Carrying Case	Cat. # 1002
Hydrotherm® Patient Unit	Cat. # 1003
BOILnSOAK® Solution	Cat. # 1004
Pliagel® Sterile Cleaner (optional) or	Cat. # 1005
Soft/Mate® Sterile Cleaner (optional)	Cat. # 1006
Patient Instructions	Cat. # 1007

HydroCurve® Soft Lenses, Inc. *PHP (U.S. Pat. 3,721,657). Trademark of Automated Optics, Inc. Soft Lenses, Inc. is a division of Continuous Curve Contact Lenses, Inc. 8006 Engineer Road, San Diego, California 92111 • 1974 Continuous Curve Contact Lenses, Inc.

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Photographs, Charts, Tables, Bibliography, Index, 474 pages
1975. SBN 399-40045-1
LC 73-88946

LIST OF CONTRIBUTORS:

The Use of Ultrasound in Neurology by D. Naldrett White, M.D.

Ultrasound Cardiography by Inge Elder, M.D.

Ultrasonography of the Abdomen and the Extremities by Joseph H. Holmes, M.D., Med. Sc.D.

The Use of Ultrasonography in Obstetrics and Gynecology by Louis M. Hellman, M.D., Ellen Cromb, R.N., Mitsunao Kobayashi, M.D., Lewis Fillisti

Principles of Doppler Ultrasound by John M. Reid, M.D., Donald W. Baker

Doppler Ultrasound in Medical Diagnosis by Ross E. Brown, M.D.

Pulse Echo Ultrasonographic Technology by Walter Strother

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Name_____

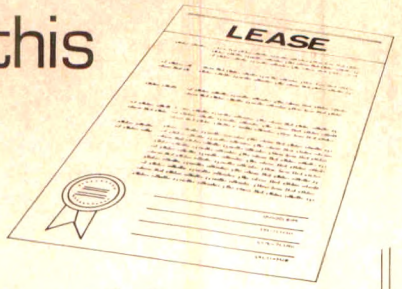
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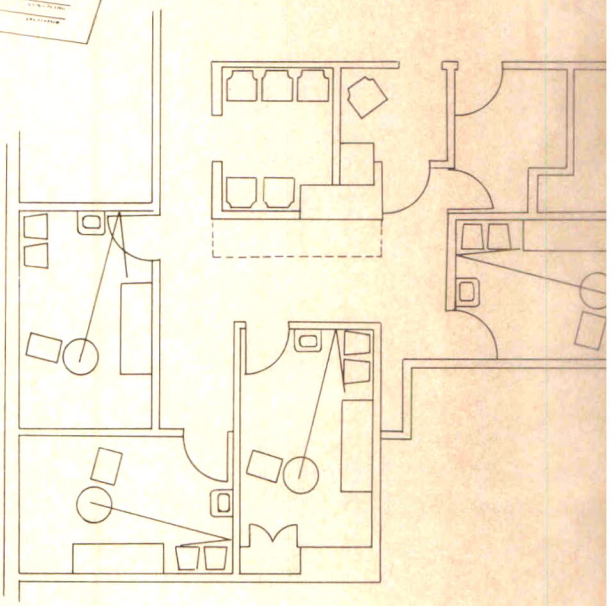
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SUBURBAN MEDICAL BUILDING, INC.

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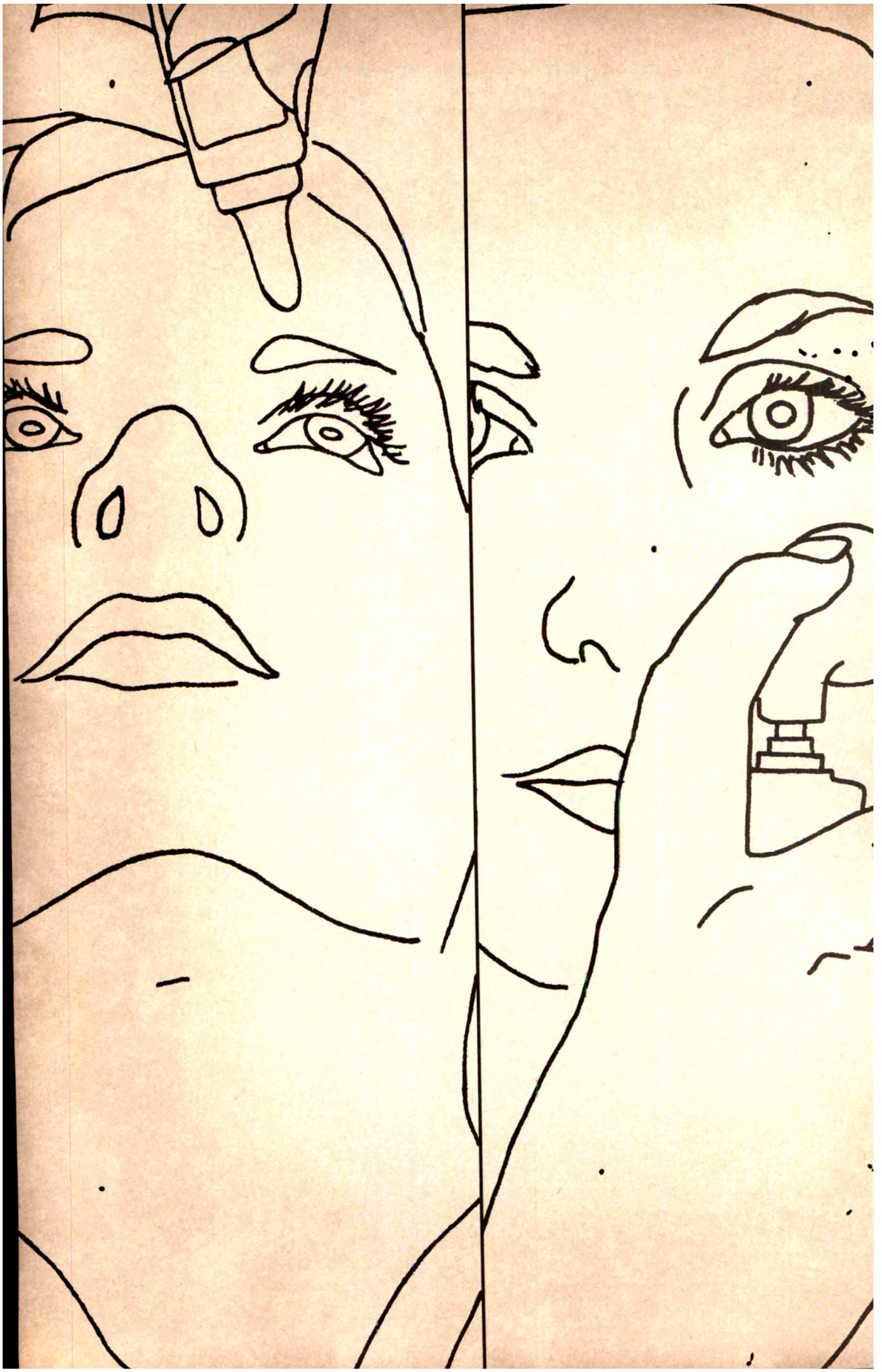
Plumbing:	$2,150.00
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Without a detailed plan of your new office as you envision it, there's no way to foresee all the expenses that will be involved in leasehold improvements. Yet once you've signed the lease, any details not included may be at your expense. Which means you could find yourself paying thousands of dollars for unexpected "extras." • We've been helping eye doctors avoid unpleasant surprises like this for over forty years, through our custom office planning service. It works quite simply: • From the Office Planning Kit we provide, you send us a form listing your specific requirements. We then submit to you a preliminary office plan based on these requirements. Upon receipt of your comments, any requested changes are incorporated into the final plan, which is complete right down to the last detail of equipment, electrical, plumbing and cabinetry. • Besides assuring most efficient use of space, this comprehensive office plan has another important advantage: when made an exhibit to your lease before it's signed, it eliminates any question about what leasehold improvements are included. • Like our complete one-source service on everything you need to equip and furnish your office, our Office Planning Kit is designed to save you time, money and headaches. Why not write or phone today for yours.

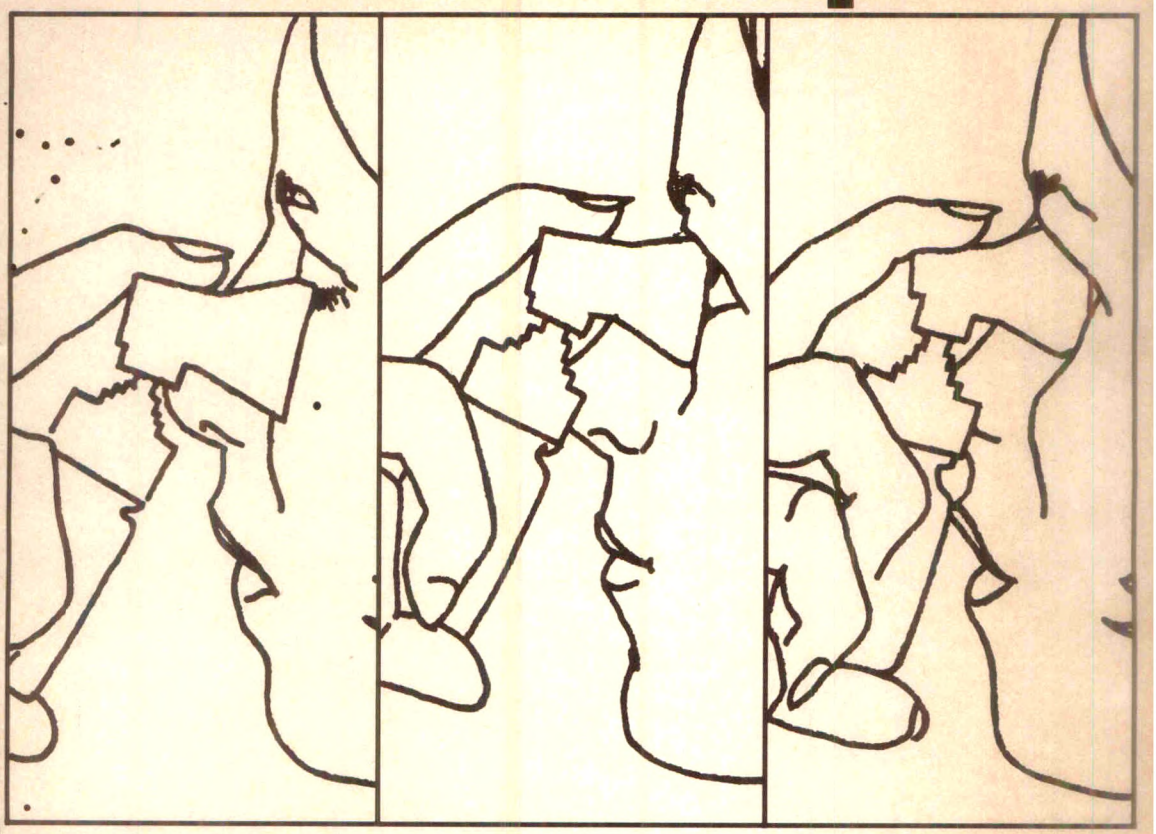
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A better way to take a drop?



Hold MISTURA between index finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone. Look up within the eye-scope.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.

Used properly, MISTURA can assure complete coverage of the absorbing surface of the eye. Its supraorbital fit avoids eye contact. MISTURA offers easy self-application, economy of full dose, on target delivery, and a minimum of wasted medication.

MISTURA®

Ophthaimic Spray Products



Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965 213-5

Please see prescribing information on last page of this advertisement

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev.7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% wi benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochlo acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflow open-angle glaucoma has been well documented. Studies have also shown that prolong topical epinephrine therapy offers significant improvement in the coefficient of aqueous o flow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facil 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful combination with miotics for the difficult-to-control patients. The addition of MISTURA E the patient's regimen often provides better control of intraocular pressure than miotics alc (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma p tients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narr angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headac conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunct and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been ported to produce macular edema in some aphakic patients and should be used with caut in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillati However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil n trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice da However, the dosage should be adjusted to meet the needs of the individual patients. This made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers proximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipi forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing b tles.

REFERENCES

1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P *pilocarpine HCl* is indicated for:

1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

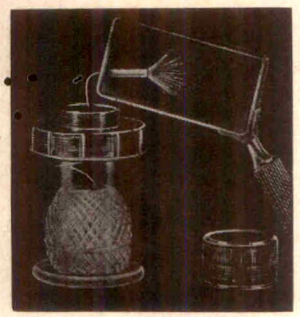
PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on prolon use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:

1. For glaucoma, the recommended dosage is 1 mist application two to four times a da the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations shoul used.
3. The dosage and strength required to reverse mydriasis depends on the cycloplegic u

When used according to the accompanying directions for use, each application delivers proximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile ml. mist dispensing bottles. Rev. 7/74

THE TISSUE-FRIENDLY

SUPRAMID EXTRA®



SUTURE. Polyfilament but neither braided nor twisted. New cable-type construction with several strands enclosed in a perfectly smooth cover of the same material, gives great pliability and superior strength. Strong, handles as silk. No stitch irritation, no growth of tissue into suture. Sizes 10-0 to 8.

AUTOCLAVABLE CONTAINERS with balls of suture suitable for repeated autoclaving for those who thread needles. Sizes 6-0 to Size 8.

SPECIAL NEEDLES: EX needle for special keratoplasties (wire size 0.2mm, length 5mm), a flattened reverse cutting needle to prevent "leaking wounds," equal to the smallest hand made eyed needles No. 82F. **The smallest spatula needle on the market, length 5 millimeters, wire size 0.20mm, double armed with 10-0, 9-0, and 8-0 black Supramid Extra. Code Nos. 2SC-100, 2SC-90 and 2SC-80.**

New: **YASARGIL NEEDLES**—for micro-neuro and micro-vascular surgery on 10-0 Black

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(4-0 Supramid Extra, double-armed with ½ curved needle):
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SUPRAMID* Quarter Globe Caps for the method by Dr. Philip Knapp.

SURGICAL SUPRAMID* MESH—for Augmentation Rhinoplasty. Reference: Beekhuis, G. Jan, M.D.: Saddle Nose Deformity, The Laryngoscope, Vol. LXXXIX, pp. 2-42, January 1974.

SUPRAMID* FOIL for plastic and reconstructive surgery; orbital floor repair, etc.
Smooth Surface Foil: 15 × 20cm, thicknesses, from 0.05mm to 2.0mm, non-sterile.
Orange-Peel Surface Foil, 0.4mm thick, 3 × 3 cm, sterile. For method by Pierre Guibor, M.D.

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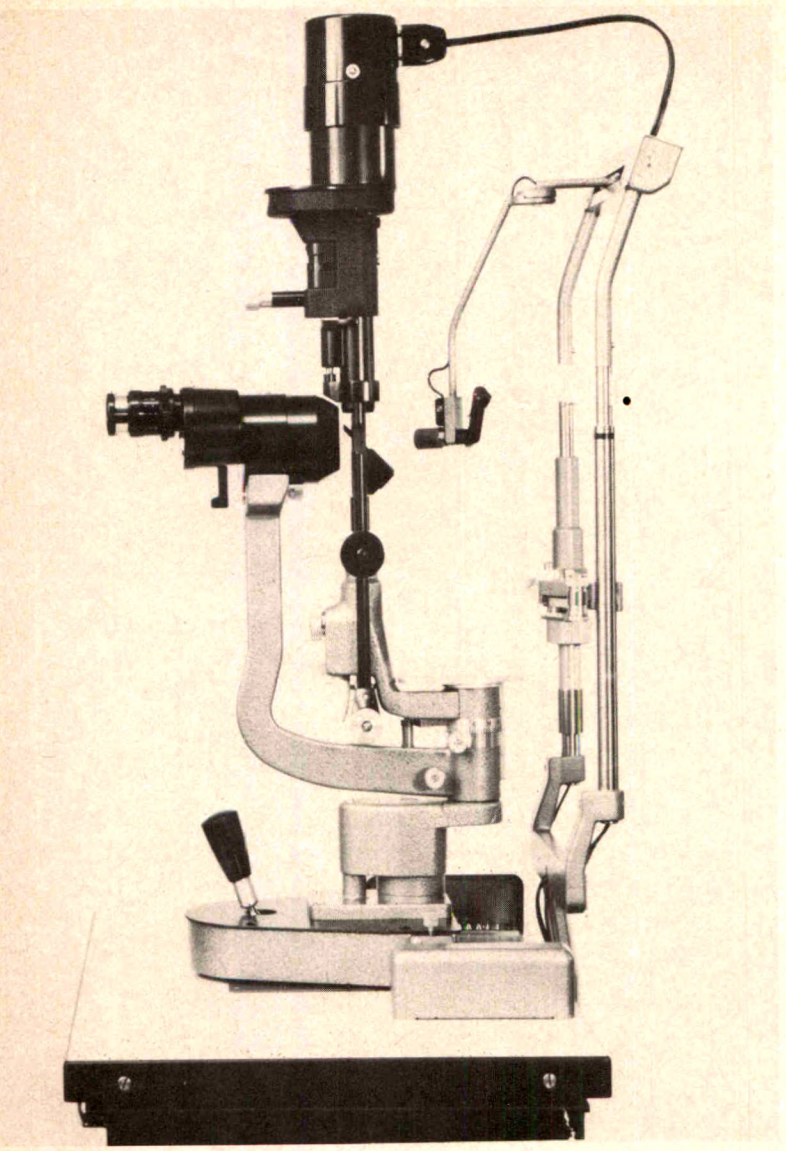
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It's the original... It's the



HAAG-STREIT Slit Lamp 900!

The value of an original is as significant in the exacting world of the healing arts as it is in the world of painting and sculpture. The Haag-Streit Slit Lamp 900 is a prime example.

The product of decades of skill and dedication to precision and reliability, the Slit Lamp 900 is made by the world's leader in ophthalmological instrumentation. It represents the kind of lifetime value that comes only with ownership of a true original.

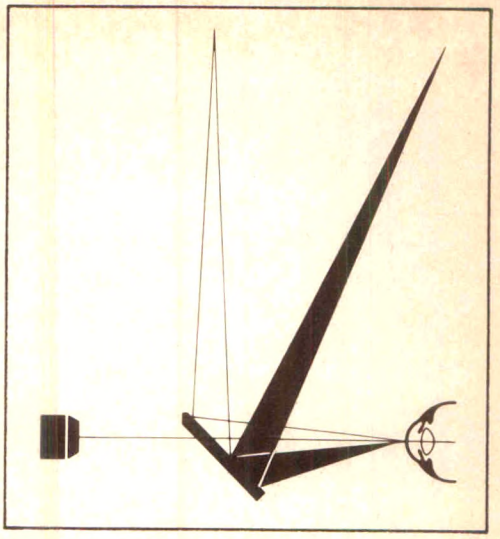
The Slit Lamp 900 is in use in every nation in the world where ophthalmology is practiced. There are approximately 10,000 of them in use in the U.S. alone. Each is an individually crafted original.

Unique in its field, the Slit Lamp 900 offers patented features which, while sometimes imitated, are not duplicated in any other instrument.

These include the three dimensional "joy stick" control lever which permits one-hand operation, and a fixation feature which allows a non-dazzling annular fixation target to be set at the patient's far point and remain in his field of view.

Available with the Slit Lamp 900 as associated equipment are the Goldmann Applanation Tonometer, Goldmann contact lenses and a full line of depth measuring and photographic equipment.

Also available from Haag-Streit is the Goldmann Perimeter 940 for kinetic and static perimetry, and the Central Scotoma device used with it. Other products include the Goldmann/Weekers adaptometer, **the Javal-Schiotz ophthalmometer and the Haag-Streit gonioscopy microscope.**



All are of the same high-quality, precision manufacture as the Slit Lamp 900, and like it . . . all are true originals.

If you are ready to make the lifetime investment that provides the value that only a true original represents, contact us or your Haag-Streit dealer. Delivery is faster than you think!

For additional information on the Slit Lamp 900 or any other Haag-Streit original equipment contact:

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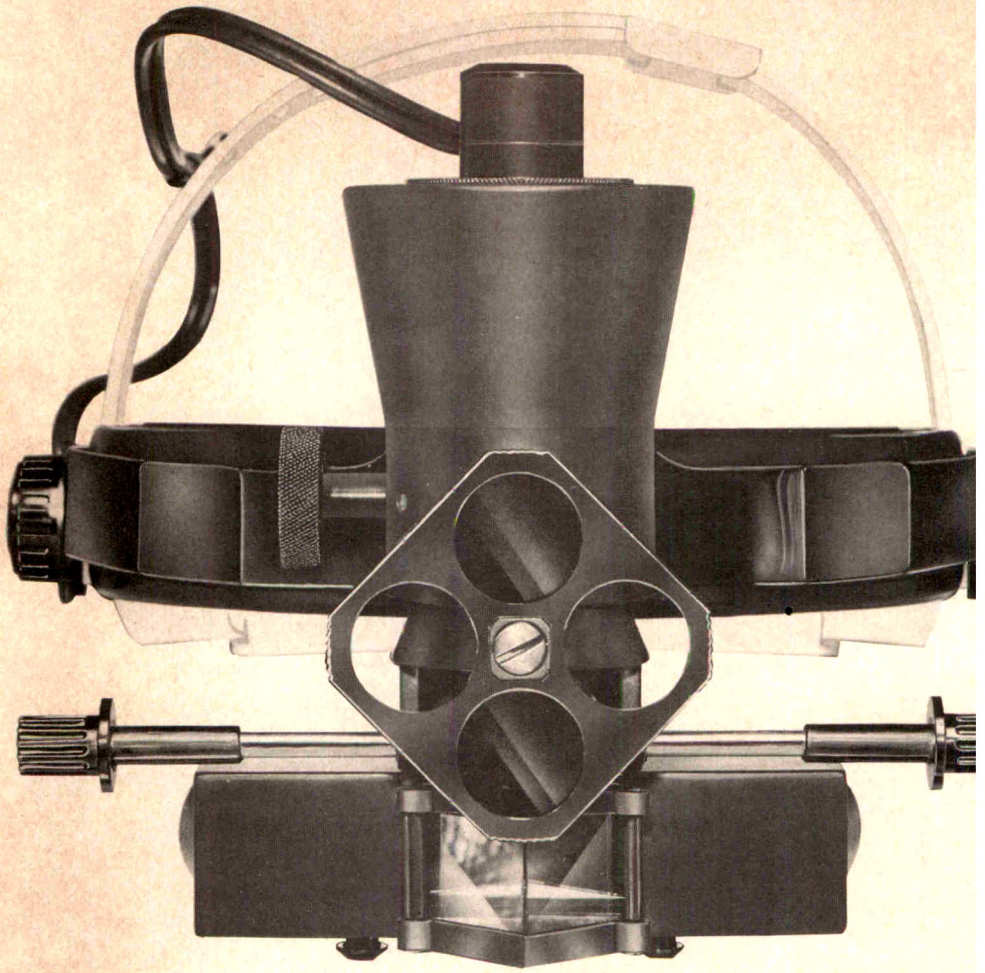
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HAAG-STREIT



The Fison Indirect Ophthalmoscope bears close examina

More than an ophthalmoscope, the Fison Indirect was designed as a com examination system—for diagnosis, teaching and surgery. Many features us considered as extras are offered as standard with the Fison. And although accessories are detachable, they are engineered as integral parts of the instru . . . and need never be removed.

Lightest, most comfortable indirect on the market. • Maximum heat dissipation th cooling cowl. • Convenient filter wheel fitted with interference red-free and blue • Optional yellow eye pieces. • Unique, hinged bi-mirror teaching attachment allows ing by two additional observers simultaneously. • Stereoscopic view and pre-fo bulb for extremely bright, clear 3D image of fundus. • Instrument and attachments able individually or as complete package.

Examine the Fison Indirect Ophthalmoscope. It should change your point of

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A sight for sore eyes. And for red eyes. And hot, scratchy eyes.



Albalon (naphazoline HCl) is an effective ocular decongestant that works fast to relieve painful, irritated, unsightly eyes. Its vasoconstricting activity lasts and lasts; for three hours or more with just one application — even with repeated insult. So Albalon gives your patients real convenience, plus the economy of fewer doses, to go along with their comfort.

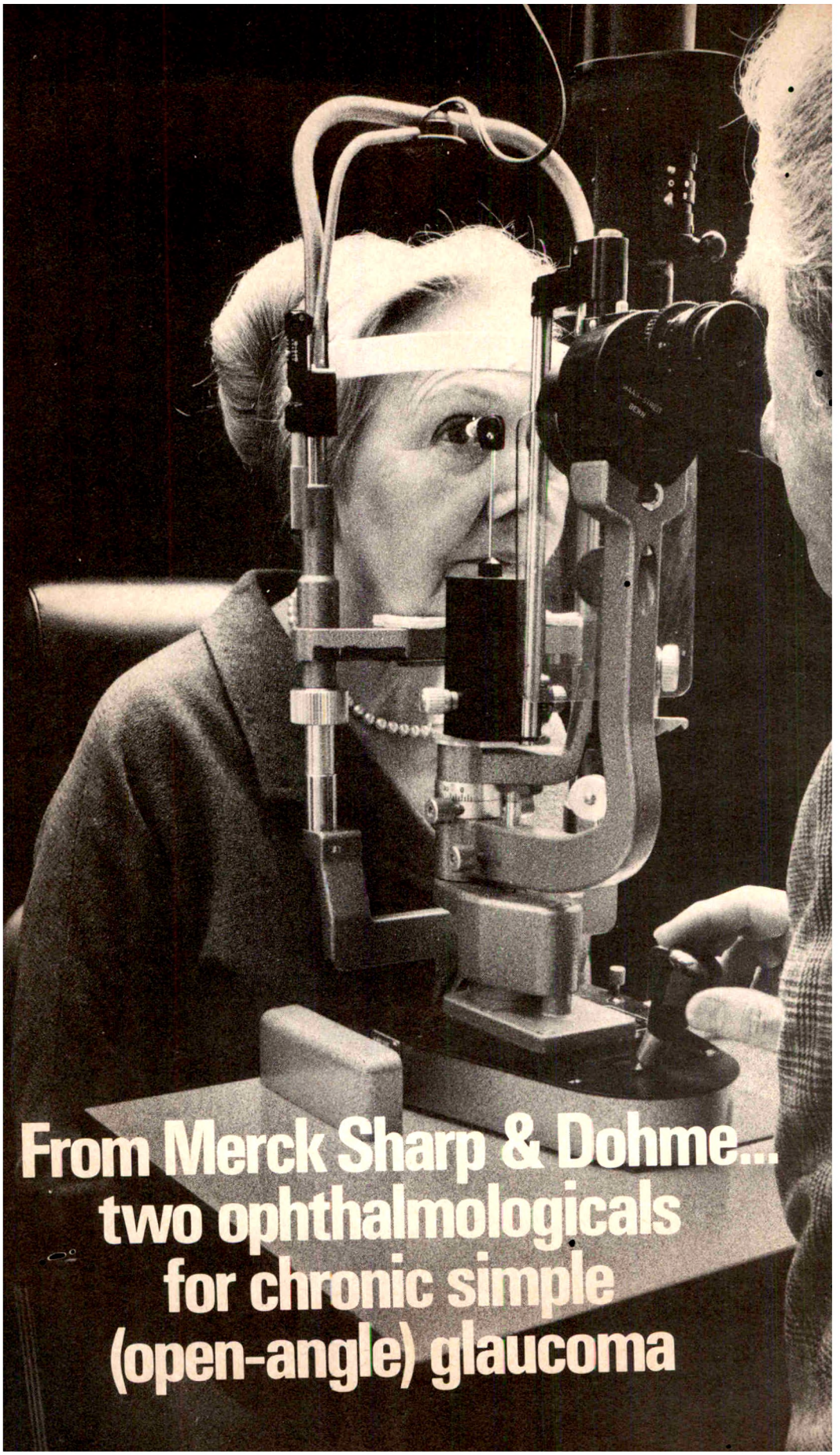
Unlike decongestants with aqueous vehicles, Albalon helps prevent corneal drying. It's formulated with soothing, protective Liquifilm® (polyvinyl alcohol 1.4%) which lubricates the eye and prolongs drug contact time.

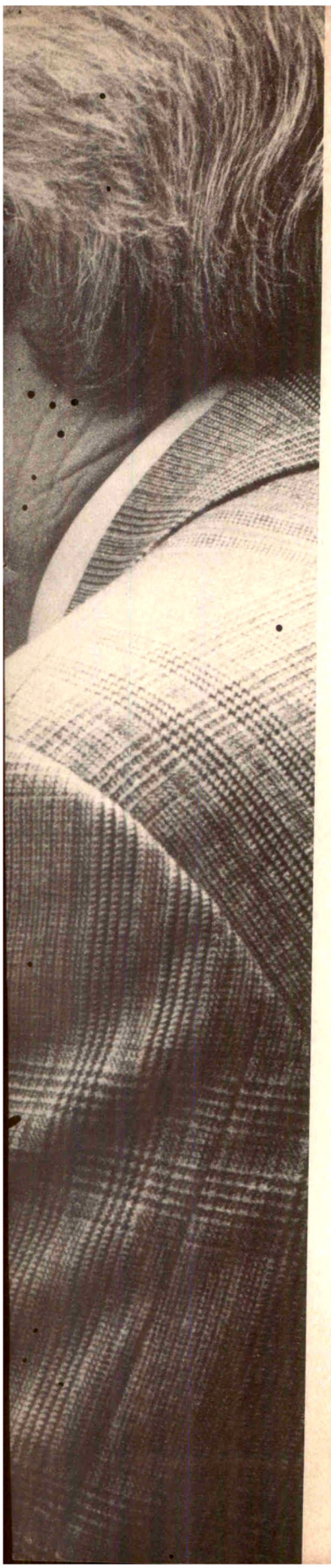
And Albalon has "Rx only" status. You determine how many refills a patient gets. So while Albalon's controlling those dry painful eyes, you're controlling Albalon.

Albalon®
(naphazoline HCl) 0.1%

INDICATIONS
For use as a topical ocular vasoconstrictor.
CONTRAINDICATIONS
Hypersensitivity to the components of this preparation.
WARNINGS
Should not be used in patients with narrow angle glaucoma. If irritation persists, or increases, discontinue use.
PRECAUTIONS
This preparation should be used only with caution in the presence of hypertension, cardiac irregularities, hyperglycemia (diabetes), hyperthyroidism.
ADVERSE REACTIONS
Pupillary dilatation, increase in intraocular pressure, systemic effects due to absorption (i.e., hypertension, cardiac irregularities, hyperglycemia).
DOSAGE AND ADMINISTRATION
One to two drops instilled in each eye every three to four hours or less frequently, as required to relieve symptoms.

ALLERGAN
Irvine, California


From Merck Sharp & Dohme...
two ophthalmologicals
for chronic simple
(open-angle) glaucoma



When a highly potent long-acting miotic is needed...

OPHTHALMIC SOLUTION, 0.125% and 0.25%

HUMORSOL®

(DEMECARIUM BROMIDE | MSD)

- Needs no refrigeration
- Needs no reconstitution
- Needs no eyedropper
- Stable at room temperature for three years

HUMORSOL is contraindicated in patients with known hypersensitivity to the drug, in active uveal inflammation, and in most cases of narrow-angle glaucoma.

When baseline miotics aren't enough...

TABLETS, 50 mg

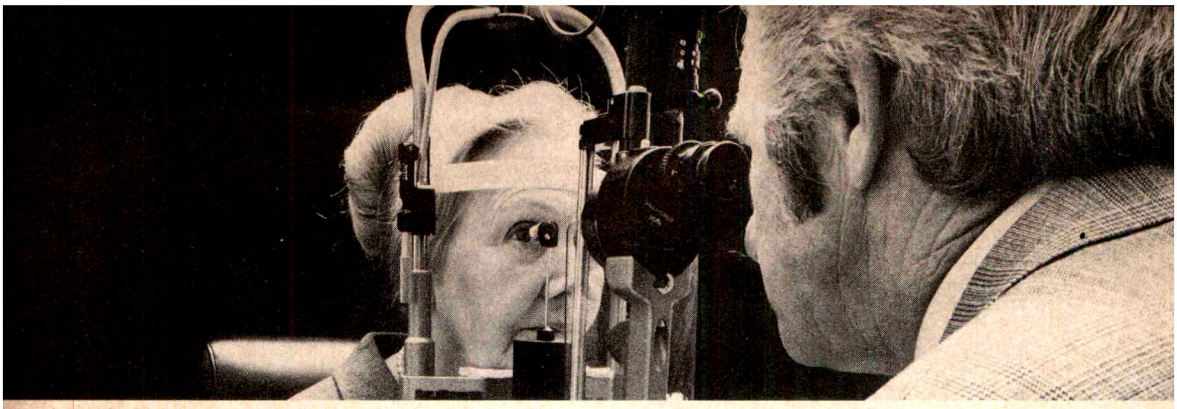
DARANIDE®

(DICHLORPHENAMIDE | MSD)

- Oral carbonic anhydrase inhibitor
- Partially suppresses secretion of aqueous humor
- Best used as adjunct to miotics
- Onset of action usually within an hour; maximal effect is observed in 2 to 4 hours
- Lowered intraocular pressure may be maintained for 6 to 12 hours

DARANIDE is contraindicated in hepatic insufficiency, renal failure, adrenocortical insufficiency, hyperchloremic acidosis, or in conditions in which serum levels of sodium or potassium are depressed. It should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased.

For brief summaries of prescribing information on DARANIDE and HUMORSOL, please see following page.



OPHTHALMIC SOLUTION, 0.125% and 0.25%

HUMORSOL®

(DEMECARIUM BROMIDE | MSD)

FOR TOPICAL APPLICATION INTO THE CONJUNCTIVAL SAC ONLY

Contraindications: Known hypersensitivity; active uveal inflammation; most cases of narrow-angle glaucoma.

Warnings: Should be administered with extreme caution to patients with myasthenia gravis who are on systemic anticholinesterase therapy; conversely, systemic anticholinesterase drugs for myasthenia gravis should be added cautiously. Succinylcholine should be administered with extreme caution before or during general anesthesia, because of possible respiratory and cardiovascular collapse.

Use in Pregnancy: Safe use in pregnancy has not been established, nor has the absence of adverse effects on the fetus or on respiration of the neonate. During pregnancy weigh potential benefits against possible hazards.

Precautions: Gonioscopy is recommended before therapy. Do not use, or use cautiously, when an intraocular inflammatory process is present.

Compression of the lacrimal sac during and following instillation for a minute or two minimizes drainage into the nasal chamber. Wash hands immediately after instillation. Discontinue use if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, or cardiac irregularities occur.

Persons exposed to organophosphate-type insecticides and pesticides (gardeners, organophosphate-manufacturing plant or warehouse workers, farmers, residents of communities which are undergoing insecticide spraying or dusting, etc.) should be warned of added systemic effects possible from absorption through the respiratory tract or skin. Wearing of respiratory masks, frequent washing, and clothing changes may be advisable.

Use with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects. Use extreme caution before intraocular surgery because of the possibility of hyphema.

Despite observance of all precautions, repeated administration may cause depression of the concentration of cholinesterase in the serum and erythrocytes, with resultant systemic effects.

Adverse Reactions: Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, brow ache, headache, and induced myopia with visual blurring; activation of latent iritis or uveitis; retinal detachment has been reported occasionally. Iris cysts may form, enlarge, and obscure vision, more frequently in children; cysts usually shrink when the miotic is discontinued but, rarely, may rupture or break free into the aqueous. Frequent examination is advisable.

Prolonged use may cause conjunctival thickening and obstruction of nasolacrimal canals. If systemic effects occur (e.g., salivation, urinary incontinence, nausea, abdominal cramps, vomiting, diarrhea, dyspnea, bradycardia, cardiac irregularities), parenteral administration of atropine is indicated: 0.4 to 0.6 mg or more for adults, proportionately less for children; artificial respiration may be required. Similar therapy is indicated for overdosage.

Lens opacities have been reported, and routine slit-lamp examinations should accompany prolonged use. Paradoxical increase in intraocular pressure may occur and be alleviated by a mydriatic.

Dosage and Administration: Initial titration and dosage adjustments must be individualized to obtain maximal therapeutic effect. Patient must be observed closely during initial period. If response is not adequate within first 24 hours, consider other measures. Keep frequency of use to a minimum in all patients, but especially in children.

Since technic is crucial to proper and safe administration, consult prescribing information for full details.

Supplied: In 5-ml OCUMETER® Ophthalmic Dispenser containing 0.125 or 0.25 percent solution and sodium chloride; benzalkonium chloride 1:5000 added as preservative.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

TABLETS, 50 mg

DARANIDE®

(DICHLORPHENAMIDE | MSD)

Contraindications: Hepatic insufficiency, renal failure, adrenocortical insufficiency, hyperchloremic acidosis, or conditions in which serum levels of sodium or potassium are depressed. Should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased.

Warning: *Use in pregnancy:* Should not be used in women of childbearing age or in pregnancy, especially during the first trimester, unless the benefits to be expected outweigh potential adverse effects.

Precautions: Potassium excretion is increased and hypokalemia may develop with brisk diuresis, when severe cirrhosis is present, or during concomitant use of steroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Hypokalemia may be avoided or treated by use of potassium chloride or giving foods with a high potassium content. Use with caution in severe respiratory acidosis.

Adverse Reactions: Side effects (characteristic of carbonic anhydrase inhibitors) may include gastrointestinal disturbances (anorexia, nausea, vomiting), loss of weight, constipation, urinary frequency, renal colic, renal calculi, mild skin eruptions, pruritus, leukopenia, agranulocytosis, thrombocytopenia, headache, weakness, nervousness, globus hystericus, sedation, lassitude, depression, confusion, disorientation, dizziness, ataxia, tremor, tinnitus, and paresthesias of hands, feet, and tongue.

How Supplied: Tablets containing 50 mg dichlorphenamide each, in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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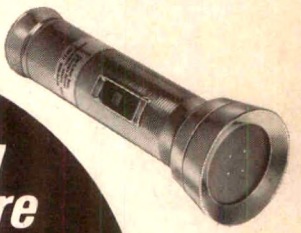
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Held by patient — leaves your hands free! For any age. Even children catch on quickly. Very difficult for patient to "cheat" when using. Attached multiple pinhole flips down easily. Made of high impact, black linen phenolic. Virtually indestructible.



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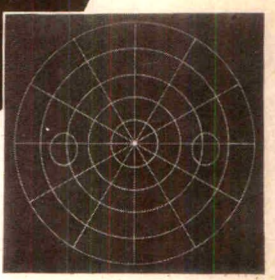
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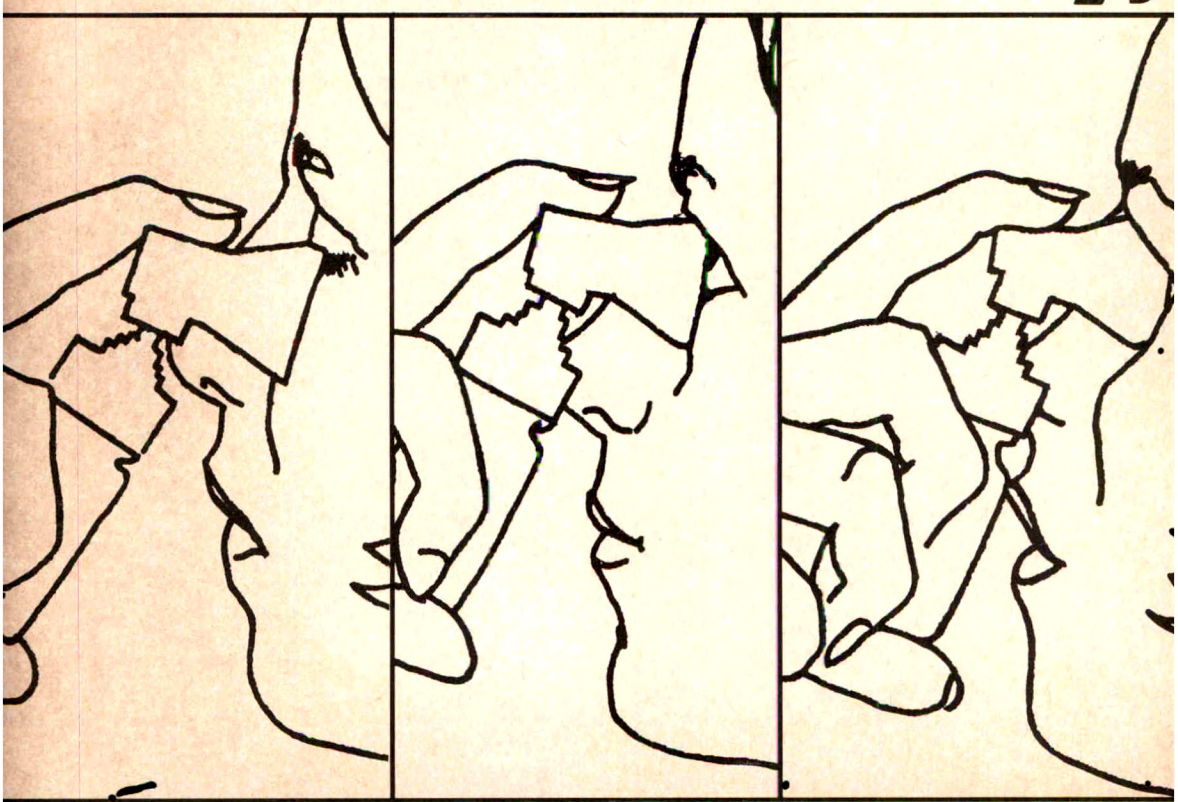
Designed by Ophthalmologists for Ophthalmologists®

Average applanation tonometry readings of 22 glaucoma patients treated first with pilocarpine drops—and then with pilocarpine mist (MISTURA® P Pilocarpine HCl).*

TONOMETRY READINGS (mm/Hg)					
On drops prior to treatment with mist		Approximately 1 month after start of treatment with mist		Two to four months after start of treatment with mist	
R. eye	L. eye	R. eye	L. eye	R. eye	L. eye
17.9	18.2	18.5	19.0	18.2	18.6
12-22	14-24	13-24	16-28	12-26	12-24

*Drug Delivery Systems for Topical Ophthalmic Medication, by G. Peter Halberg, M.D., FACS, Stephen E. Kelly, M.D., Michael Morrone, M.S., Annals of Ophthalmology, September, 1975.

Tonometrically,



Hold MISTURA between index finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone. Look up within the eye-scope.

Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.

46 patients with chronic simple open angle glaucoma who initially used pilocarpine drops and then changed to pilocarpine mist (MISTURA P Pilocarpine HCl).†

MEAN TONOMETRY READINGS (mm/Hg) AFTER TREATMENT WITH

	1% PILOCARPINE (N=16)		2% PILOCARPINE (N=30)	
Time of reading	R. eye	L. eye	R. eye	L. eye
Drops				
1st weekly visit	17	17	20	20
2nd weekly visit	16	16	20	19
Mist (MISTURA)				
3rd weekly visit	16	16	20	19
4th weekly visit	16	16	20	19

†Data on file at Lederle Laboratories.

it's a draw

A better way to take a drop?

In two recent studies,*† glaucoma patients were switched from pilocarpine drops to MISTURA® P Pilocarpine HCl. In both studies MISTURA P was shown to be therapeutically equivalent in the control of intraocular pressure.

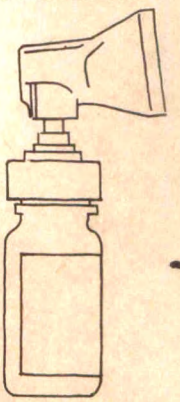
But MISTURA offers several unique advantages.

Built-in lid-retraction to suppress the blink. Easy self-application. Full dose, on target delivery to avoid wasted medication.

When you compare MISTURA to drops, consider convenience.

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Please see prescribing information on last page of this advertisement.

MISTURA®

Ophthalmic Spray Products

MISTURA® D

Phenylephrine HCl 0.12%

Ophthalmic Solution Sterile

DESCRIPTION: MISTURA D is a decongestant that whitens the eye and relieves minor eye irritations caused by hay fever, colds, dust, wind, swimming, sun, smog or hard contact lenses.
CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev 7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

l-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% with benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochloric acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow facility 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly useful in combination with miotics for the difficult-to-control patients. The addition of MISTURA E to the patient's regimen often provides better control of intraocular pressure than miotics alone. (Ballentine and Garner[2] indicated that with 80% of the uncontrolled open-angle glaucoma patients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensing bottles.

REFERENCES
1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

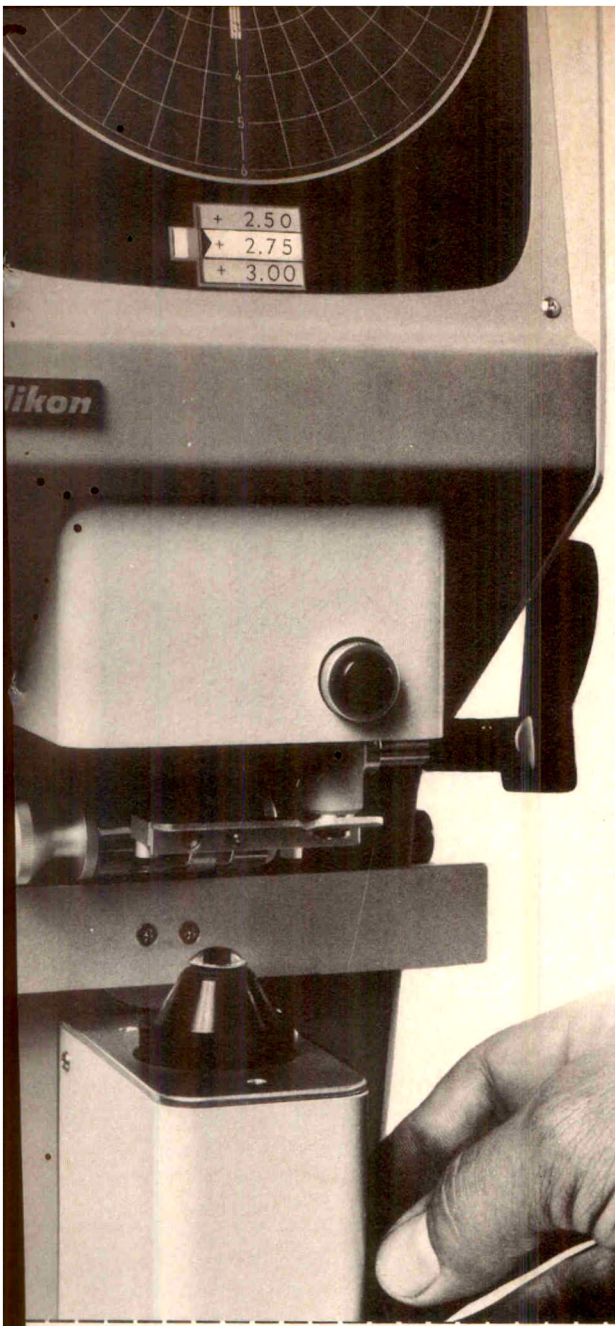
Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,000 as preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P *pilocarpine HCl* is indicated for:
1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on prolonged use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:
1. For glaucoma, the recommended dosage is 1 mist application two to four times a day of the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations should be used.
3. The dosage and strength required to reverse mydriasis depends on the cycloplegic used.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in sterile 15 ml. mist dispensing bottles. Rev. 7/74



Nikon takes the jelly out of soft lens inspectio

One of our customers recently remarked. "When check a soft lens with an ordinary focimeter, it's trying to inspect a piece of jelly." But that's not case with the Nikon Projection Vertexometer.

Because of the instrument's vertical configurat you don't have to be a contortionist to check dio value of a lens. Simply blot it, place it on the lens ta and focus the crosslines on the Vertexometer's pro tion screen. Back vertex power automatically appe in numerals in the diopter scale window.

"What's more," observed Jim Vilardi, Manager of Ophthalmic Division, "in addition to measuring dio value, you can also check the quality of a soft lens evaluating the image on the Vertexometer's bright f inch diameter target."

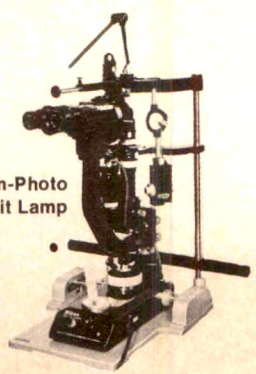
This instrument offers a host of features which c tribute to accuracy of measurement and speed of eration. For example, the bright, crisp target im can be viewed in a normally lighted room. The wheel permits 360° endless rotation. Measurem range is ±25 diopter in increments of 0.25 D. And termediate calibrations appear within the ±3.00 ra to indicate the 0.125 diopter position. But to fully preciate the instrument's capabilities, you'd have read our technical brochure. And we hope you will.

Write or phone for details on the Vertexometer. Yo find it makes inspection of soft lenses as simple checking glass lenses. We'll also be happy to sup information on our entire line of ophthalmic produ Nikon Inc., Instrument Group, Ophthalmic Div., Ehr reich Photo-Optical Industries, 623 Stewart Aven Garden City, New York 11530. (516) 248-5200.

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Affiliation_____

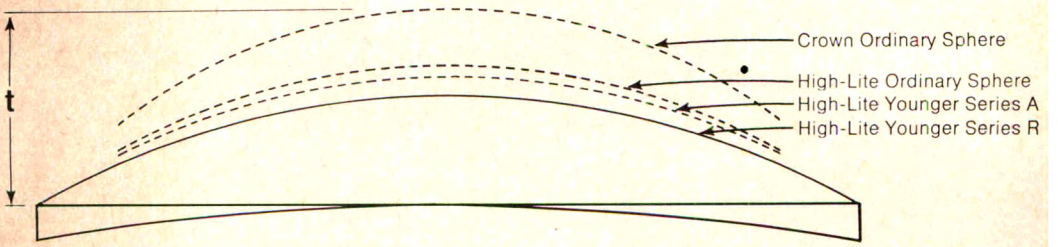
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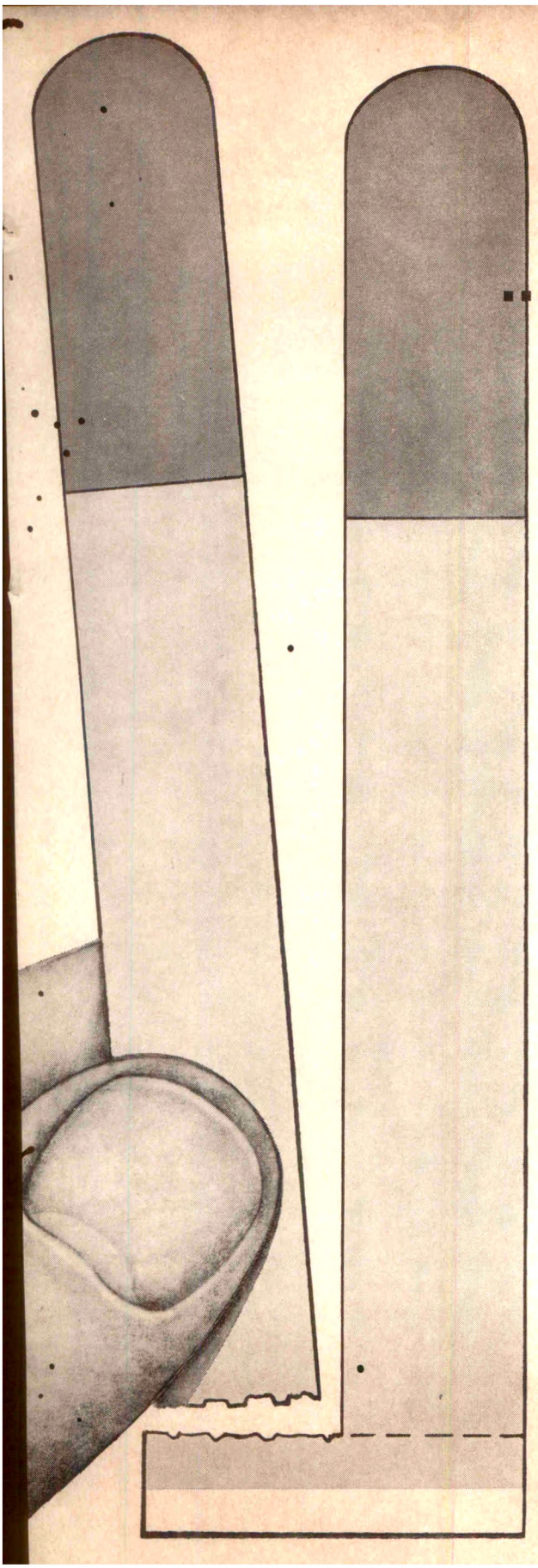
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DESCRIPTION	t = CENTER THICKNESS
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Easy to use: simply retract the upper lid, apply the dry orange tip of the flexible applicator to the bulbar conjunctiva at the temporal side.



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(sodium fluorescein)

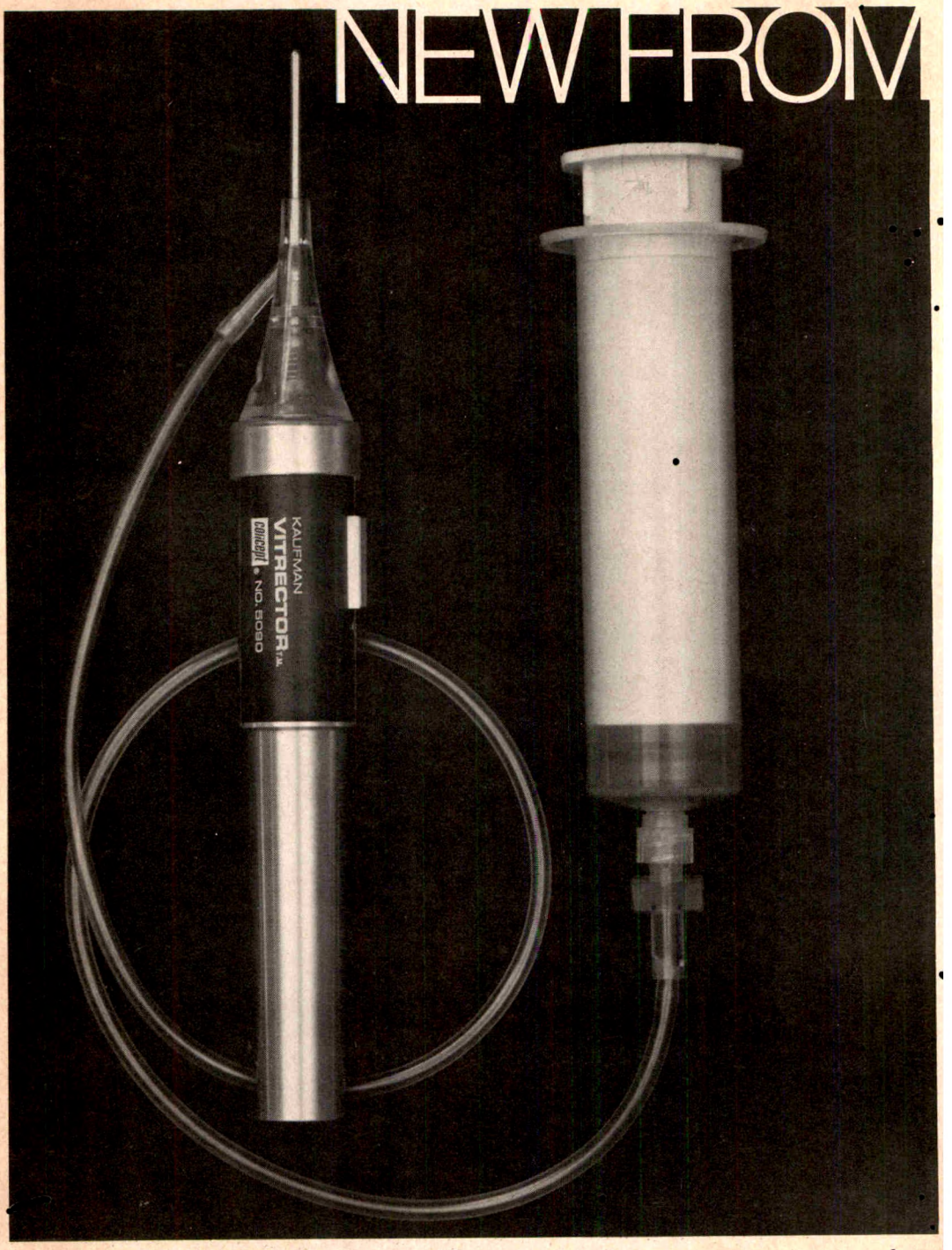
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HOUSE OF VISION

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The Vitrector consists of a reusable, battery powered unit and a separate, sterile disposable unit consisting of cutting head, plastic syringe and suction tube. Also included with each kit is a latex sleeve which easily slips over the power unit for reuse without sterilization. The cutting head, suction syringe and plastic tube are disposable, and should *not* be resterilized or autoclaved as reuse may be hazardous.

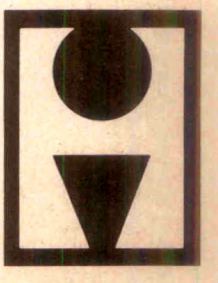
If vitreous loss occurs, just slip the power unit into the latex sleeve, snap on the cutting head and connect the suction tube and syringe. The assistant can observe the vitrectomy, and using the syringe apply just the right amount of suction.

AVAILABLE FOR IMMEDIATE DELIVERY FROM STOCK

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PDR
1975/6

Table of Contents

PRACTICES IN OPHTHALMOLOGY 4

This section contains a summary of current practices in opthalmology, prepared by Paul Henkind, M.D., Ph.D., Alan H. Friedman, M.D. and Arthur W. Berger, O.D. of the Albert Einstein College of Medicine in New York. The clinical applications of ophthalmic pharmaceuticals plus data on ophthalmic lenses, sutures, needles and low vision devices discussed here.

INDICES 101

This section, divided in five parts—Manufacturers' Index, Brand Name Index, Generic Name Index, Drug Classification Index and Instrumentation Index—is cross-referencec to simplify location of desired product information.

PRODUCT INFORMATION 201

This section is divided in two parts—Part I, Pharmaceutical Products and Part II, Lens Care Products. Products are listed alphabetically by manufacturer. The information concerning the products described in this section has been prepared by the manufacturer, and edited and approved by the medical department, medical director, or medical counsel of each manufacturer.

INSTRUMENTATION and EQUIPMENT 301

This section is divided into three parts: Part I—Specialized Instruments and Equipment; Part II—Lenses; Part III—Sutures. Participating companies have described or listed categories of products manufactured along with the locations of their sales and service offices. Additional information about these companies and their products and services may be solicited by using the enclosed Reader Service Card.

EDUCATIONAL MATERIAL 401

This section alphabetically lists publishers and books available pertaining to the practice of ophthalmology. Current prices are included and a Reader Service Card is enclosed for your purchasing convenience.

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(l-epinephrine) ophthalmic solution
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Indications: Chronic simple glaucoma.

Contraindications: Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack.

Warnings: Undesirable side reactions may include: eye pain or ache, blurred vision, headache, conjuctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients and should be used with caution in these patients.

Precautions: Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases.
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Dosage and Administration: The usual dosage is 1 drop in the affected eye(s) once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with Epifrin available in four strengths.
Note: Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded.
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Bascom Palmer Eye Institute
University of Miami School of Medicine
Miami, Florida

FRANCIS A. L'ESPERANCE, M.D.
Assistant Professor of Clinical Ophthalmology
Edward S. Harkness Eye Institute
Columbia University College of Physicians and Surgeons
New York, New York

RUDOLF KLOTI, M.D.
Clinical Assistant Professor of Ophthalmology
University Eye Clinic
Zurich, Switzerland

ROBERT MACHEMER, M.D.
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Professor
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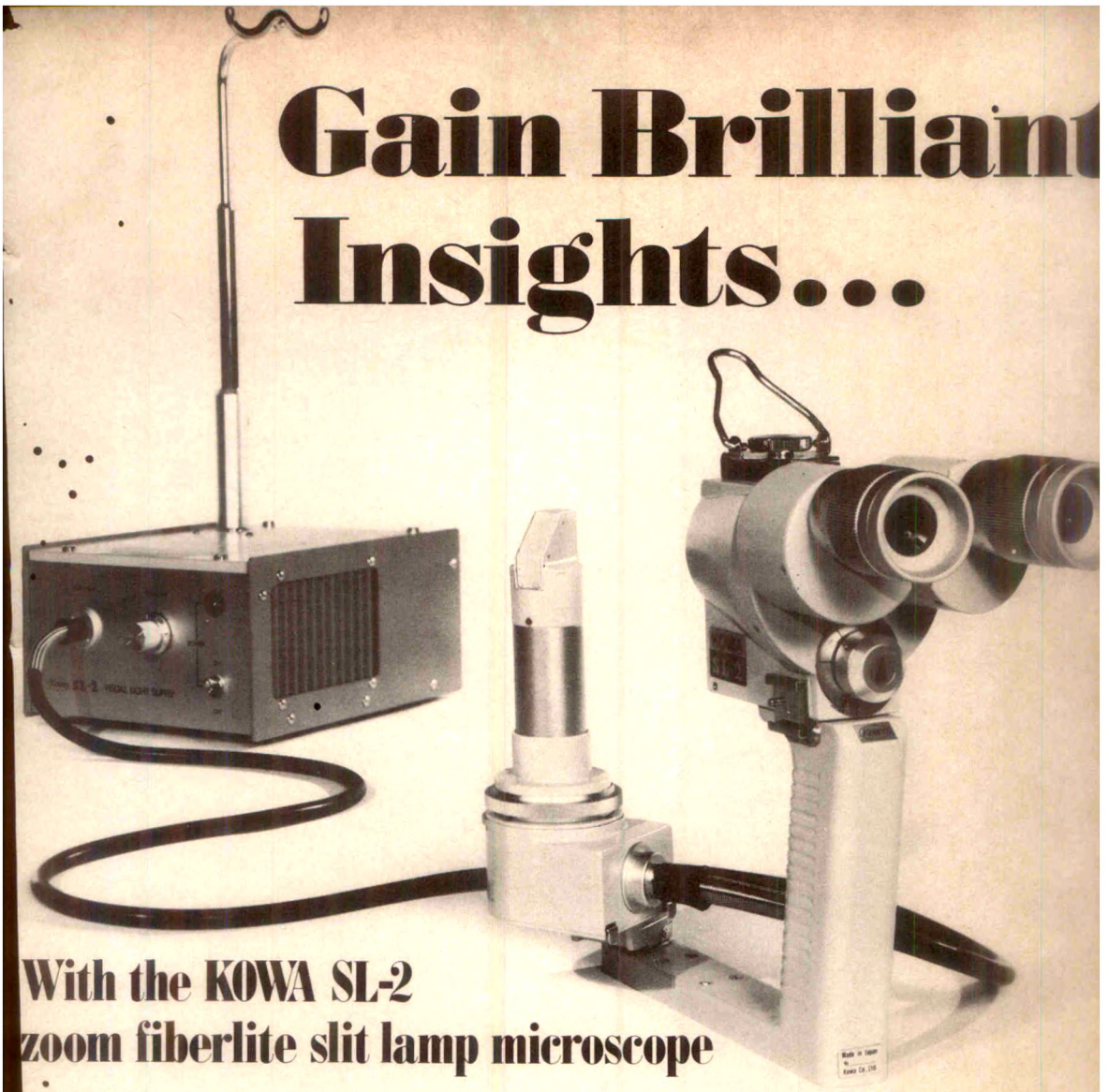
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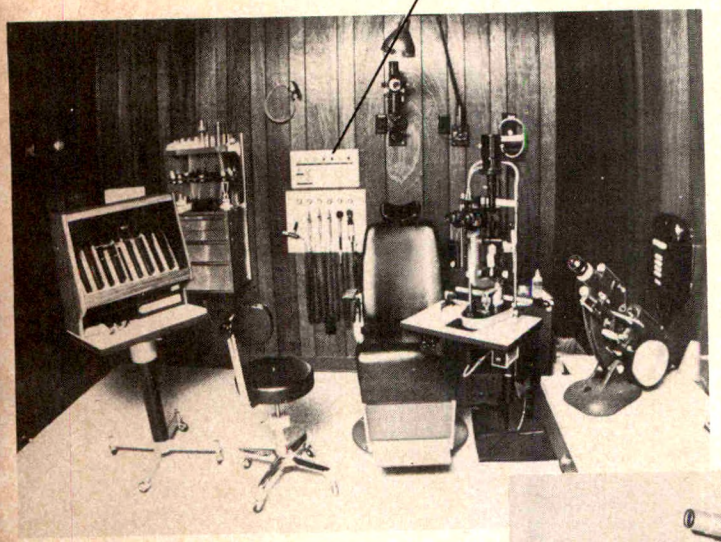
Touch a button under the slit lamp—it is read use as the room lights instantaneously dim. Li indirect ophthalmoscope and the room lights g

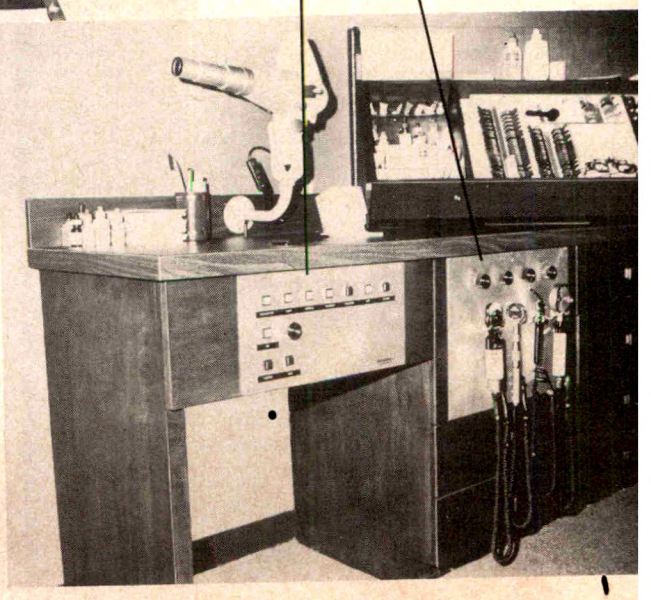
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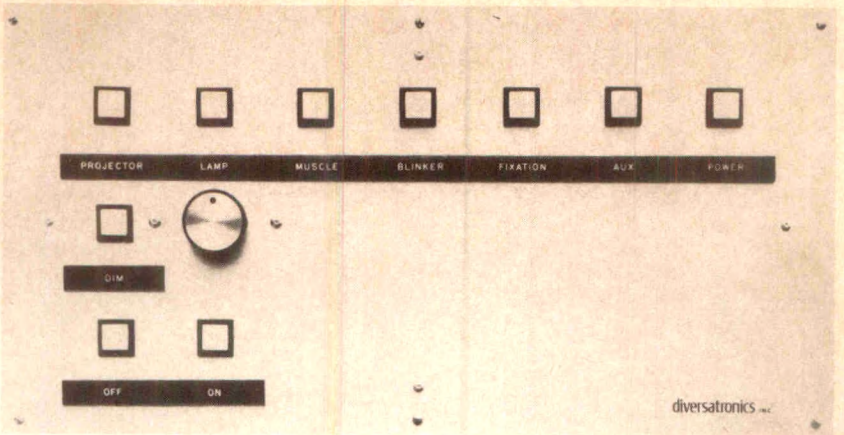
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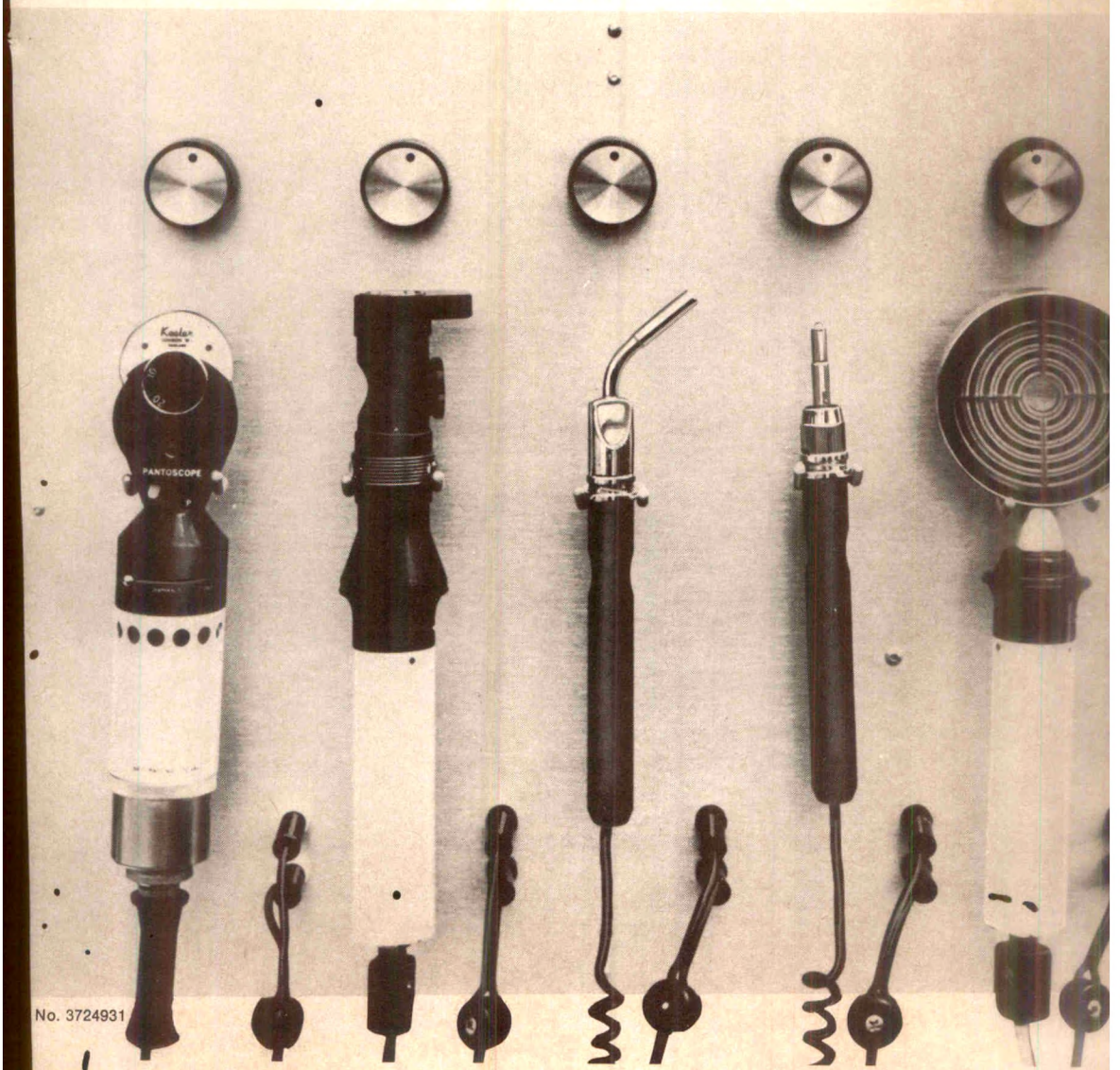




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INTRAOCULAR LENS MEETING
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(Registration will start Thursday, January 29, 1976, 5-9 p.m.
Meeting will start Friday at 9:00 a.m. and will end Sunday at 1:00 p.m.)

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COURSES

Course No. 1
Elementary Hard and Soft Contact Lens Fittings
Course Director: G. Peter Halberg, M. D.
Instructors: To Be Announced

Course No. 2
Therapeutic Lenses and Scleral Shells
Course Director: Herbert L. Gould, M.D.
Instructors: John W. Espy, M.D., Marsha Guibor

Course No. 3
Conventional Corneal Lenses: Fitting Principles and Problem Management
Course Director: Perry Rosenthal, M.D.
Instructors: To Be Announced

Course No. 4
Soft Contact Lens Fitting with Custom Designed Lenses
Course Director: Paul R. Honan, M.D.
Instructor: Herschell H. Boyd, M.D.

Course No. 5
Bifocal and Unifocal Contact
Lenses for the Presbyope
Course Director: Abraham Schlossman, M.D.
Instructors: Charles E. Clevenger, M.D., George H. Jones, M.D., George B. Pugh, M.D., Carolyn Schlossman, Norman Schmid, Sr., Frank Weinstock

Course No. 6
Therapeutic Hydrophilic Soft Lenses
Course Director: James V. Aquavella, M.D.
Instructors: Joseph A. Baldone, M.D., S. Arthur Boruchoff, M.D., John W. Espy, M.D., Richard H. Keates, M.D., Anthony B. Nesburn, M.D.

Course No. 7
Technological Aspects of Hard and Soft Contact Lenses (Basic Course—Instrumentation, Basic Lens Design, Modification and Follow-up Visits)
Course Director: Joseph Soper
Instructors: Frank Sanning, Kenneth Swanson, Ralph Sutton

Course No. 8
Aphakia—Lens Choice and Management
Course Director: Robert J. Crossen, M.D.
Instructors: Thomas R. Mazzocco, M.D., Robert C. Welsh, M.D.

Course No. 9
Clinical Aspects of Fitting the HydroCurve^{tm} Lens
Course Director: James S. Russell, M.D.
Instructor: Susan Savage

Course No. 10
Cosmetic Fitting with the Bausch & Lomb Soflens
Course Directors: Ellis Gruber, M.D. and Charles O. Titus, M.D.
Instructors: To Be Announced

Course No. 11
Present Status of Silicone Lenses
Course Director: Chester J. Black, M.D.
Instructors: To Be Announced

Course No. 12
Hard and Soft Lenses in the Treatment of Ocular Pathology
Course Director: Frank B. Hoefle, M.D.
Instructors: Jorge N. Buxton, M.D., James Koverman

Course No. 13
Hard Contact Lenses
Course Director: Herschell H. Boyd, M.D.
Instructor: Paul R. Honan, M.D.

Course No. 14
Basics of Hydrophilic Lens Fitting—A Canadian Approach
Course Director: John F. Morgan, M.D.
Instructors: Ronald E. Groshaw, M.D., Bernard J. Slatt, M.D., Harold A. Stein, M.D., John D. Valberg, M.D.

Course No. 15
Orthokeratology
Course Director: Donald A. Fonda, M.D.
Instructors: Richard S. Fixott, M.D.

Course No. 16
The Use of Therapeutic Soft Contact Lenses
Course Director: Robert G. Webster, Jr., M.D.
Instructors: Walter J. Stark, M.D., H. Lee Stewart, M.D.

Course No. 17
Intraocular Lens Surgery, Indications and Contra-indications, Surgical Techniques
Course Directors: Jack Hartstein, M.D. and Richard P. Kratz, M.D.
Instructor: Herbert L. Gould, M.D.

Course No. 18
Surgical Aspects of Contact Lens Patients
Course Director: Pierre Guibor, M.D.
Instructors: Robert A. D'Amico, M.D., Marsha Guibor, Richard C. Troutman, M.D.

Course No. 19
Basic Fitting Technique and Workshop with the Warner-Lambert Softcon Lens
Course Director: Edward Shaw, M.D.
Instructors: To Be Announced

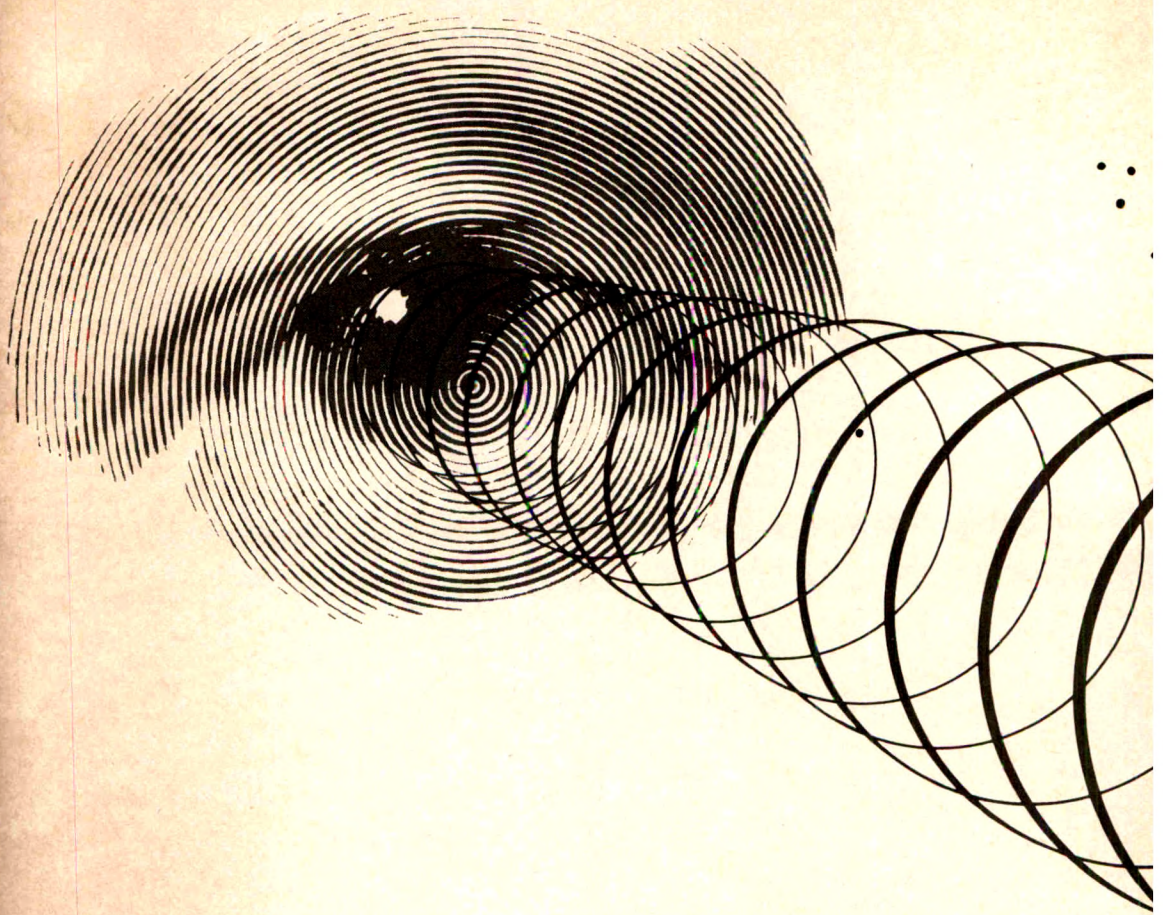
Course No. 20
Aphakic Correction
Course Director: Robert C. Welsh, M.D.
Instructors: Robert J. Crossen, M.D., Herbert L. Gould, M.D., Thomas R. Mazzocco, M.D., Charles Moore

INTRAOCULAR LENS COURSES, Sunday, February 1, 1976, 7-9 A.M.

Six intraocular lens courses will be given. The intraocular lens courses are so arranged that they will not conflict with the remainder of the courses.

Intraocular Lens Course Instructors are: James V. Aquavella, M.D., Stanley C. Becker, M.D., Jorge N. Buxton, M.D., Herve M. Byron, M.D., Robert C. Drews, M.D., Jack Hartstein, M.D., Francis C. Hertzog, Jr., M.D., Kenneth J. Hoffer, M.D., Herbert E. Kaufman, M.D., Richard H. Keates, M.D., Richard P. Kratz, M.D., David M. Worthen, M.D.

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primate trabecular meshwork (X30

Viewed here is Schlemm's ca
along with uveal and corneoscle
meshwork. (Photo court
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This area is the site of the pri
pathologic changes which
responsible for glaucoma and
focus of most of the med
procedures for treatment of the disea

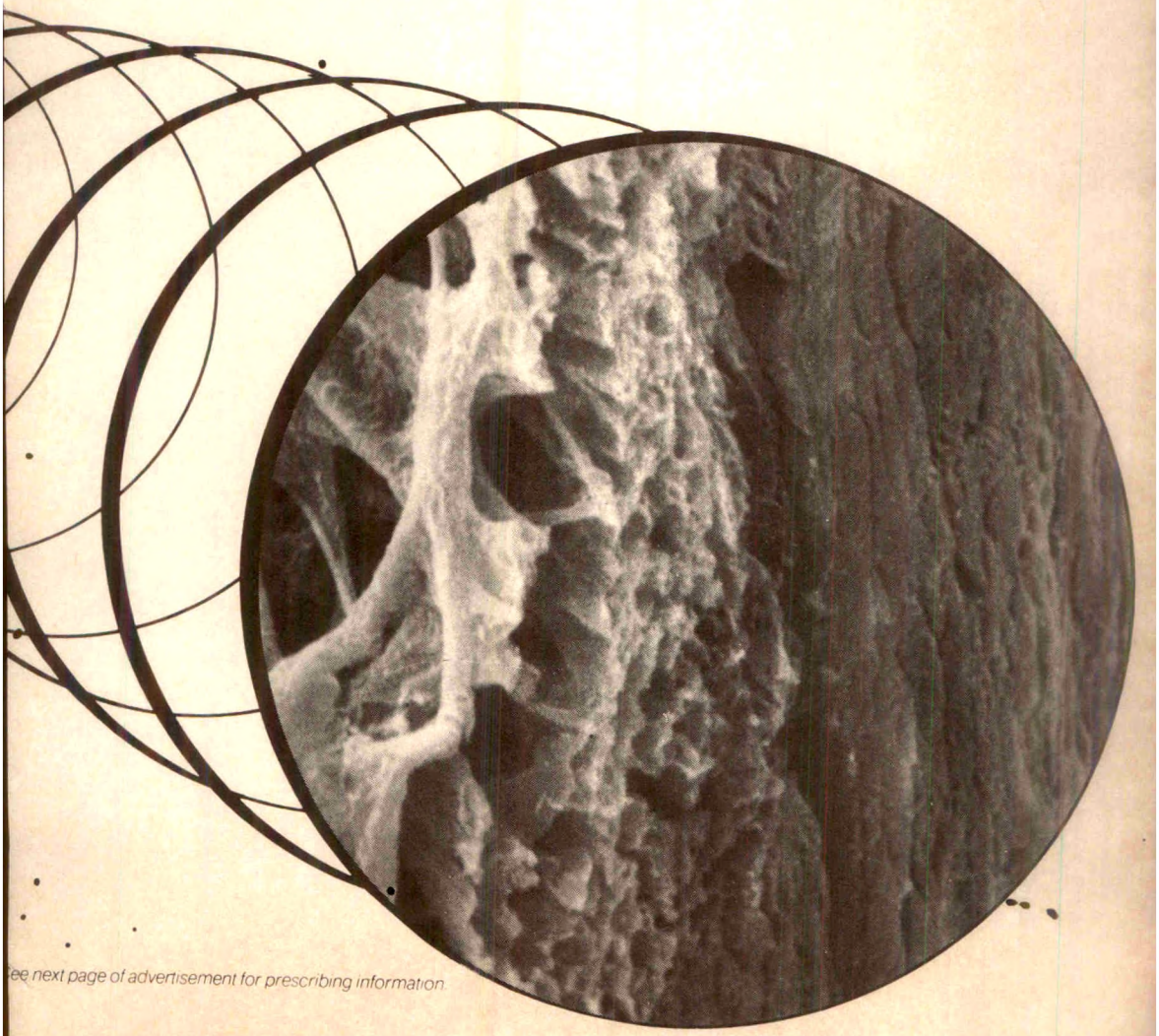
Because PHOSPHOLINE IODIDE is long-acting, it can help provide uninterrupted control of intraocular pressure in chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia. Just one or, at most, two instillations of PHOSPHOLINE IODIDE (one at bedtime, and, if necessary, one in the morning) are generally needed.

Although PHOSPHOLINE IODIDE is longer-acting than other miotics, it is *not* more potent. With four concentrations available, it offers a high degree of dosage flexibility for uninterrupted control of intraocular pressure...used alone or in combination with other medication.

When starting PHOSPHOLINE IODIDE therapy, 0.03% – the lowest strength – is the logical choice. If strengths of 0.06%, 0.125%, or 0.25% are required, the initial use of the 0.03% will be helpful in smoothing the transition.

PHOSPHOLINE IODIDE® not more potent... but longer-acting

(echothiophate iodide for ophthalmic solution)



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PHOSPHOLINE IODIDE®
(echothiophate iodide)
in the management of chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia

BRIEF SUMMARY
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PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
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Accommodative esotropia—Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

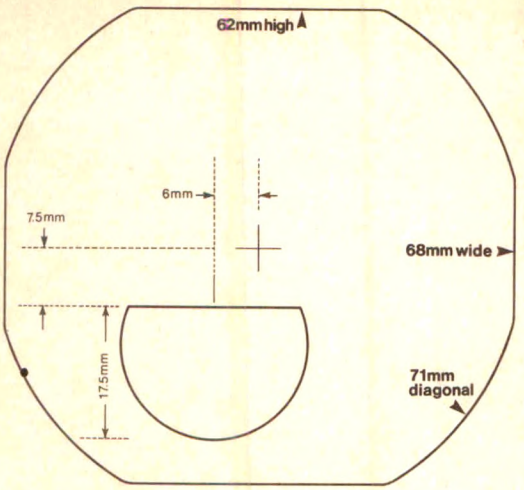
6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.]

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A. *NEURO-OPHTHALMOLOGY SYMPOSIUM*

January 6-9, 1976

Diseases of the Optic Nerve and Chiasm
Disturbances of Ocular Motility
Neuro-physiology of Vision

Guest Lecturers

Dr. Alan Bird
Dr. David Cogan
Dr. William Hoyt
Dr. Alfred Huber
Dr. Norman Schatz
Dr. George Udvarhelyi
Dr. Frank Walsh

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B. *STRABISMUS*

January 9

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Dr. Sal Can
Dr. Edward
Dr. Alfred
Dr. Arthur
Dr. Marshal
Dr. John P

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C. *VITREOUS-RETINAL-CHOROIDAL SYMPOSIUM*

January 12-15, 1976

Present Concepts in Diagnosis and Treatment of Malignant Melanoma of
Macular Diseases—Diagnosis and Treatment
Role of Vitreous Surgery in Perforating Injuries

Guest Lecturers

Dr. Thomas Aaberg
Dr. Pierre Amalric
Dr. Alan Bird
Dr. August Deutman
Dr. Ricardo Dodds
Dr. Nicholas Douvas
Dr. Robert Ellsworth
Dr. Rudolph Kloti
Dr. Edward Maumenee
Dr. Ronald Michels
Dr. H. Neubauer
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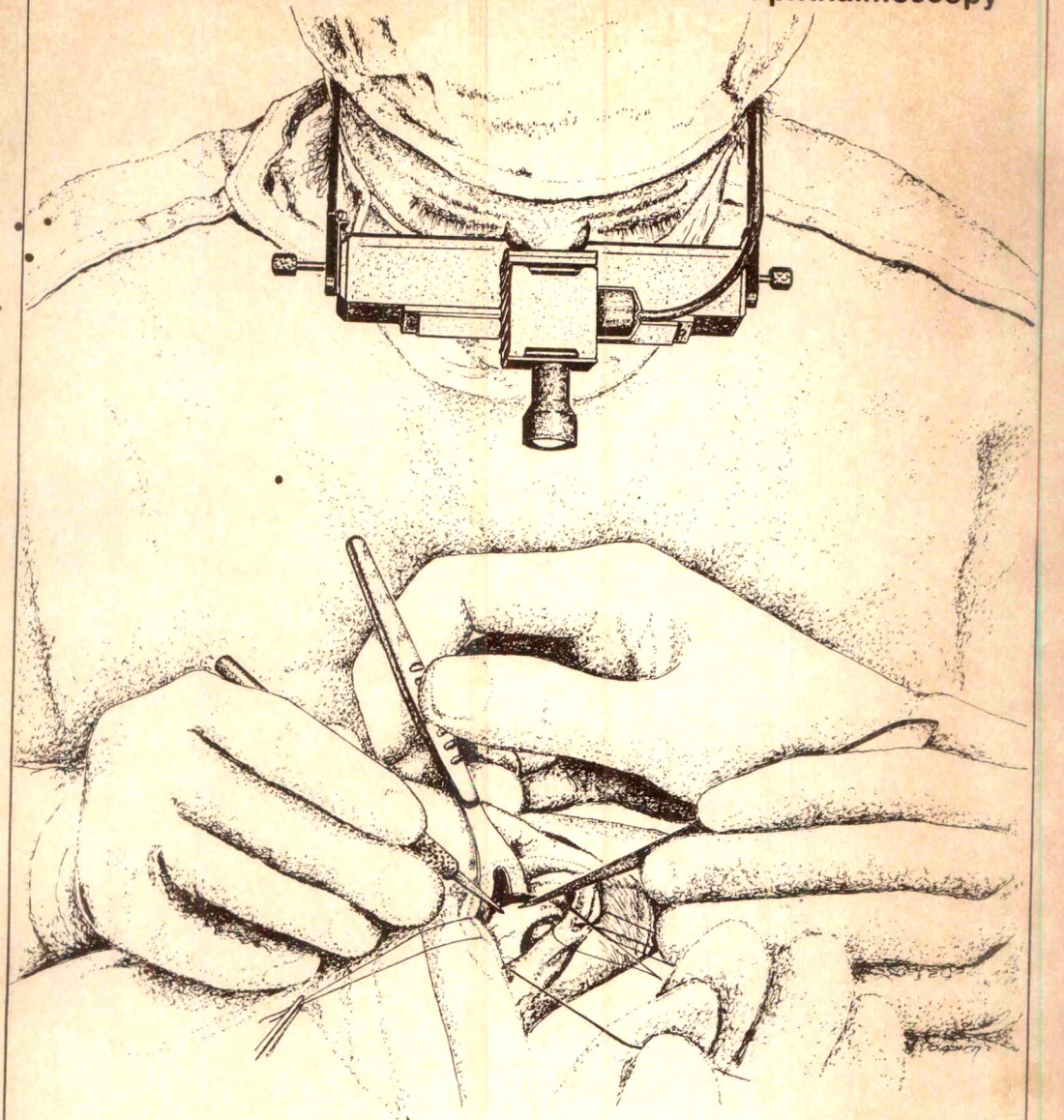
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The Bedell Lecturer will be David Shoch, M.D., Chairman of the Department of Ophthalmology of Northwestern University.

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Inquiries should be addressed to Gerard Shannon, M.D., Chairman, Annual Clinical Conference Committee.

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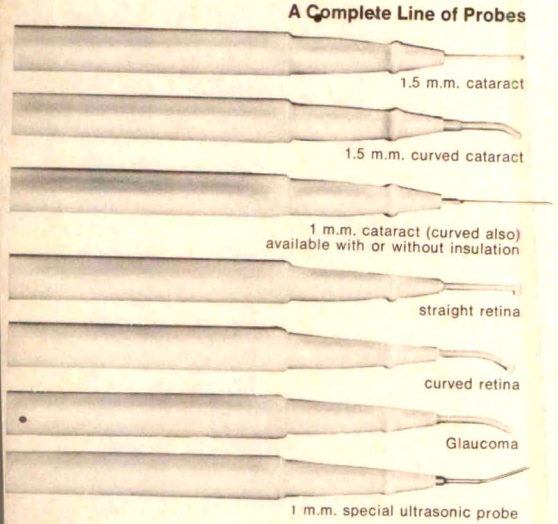
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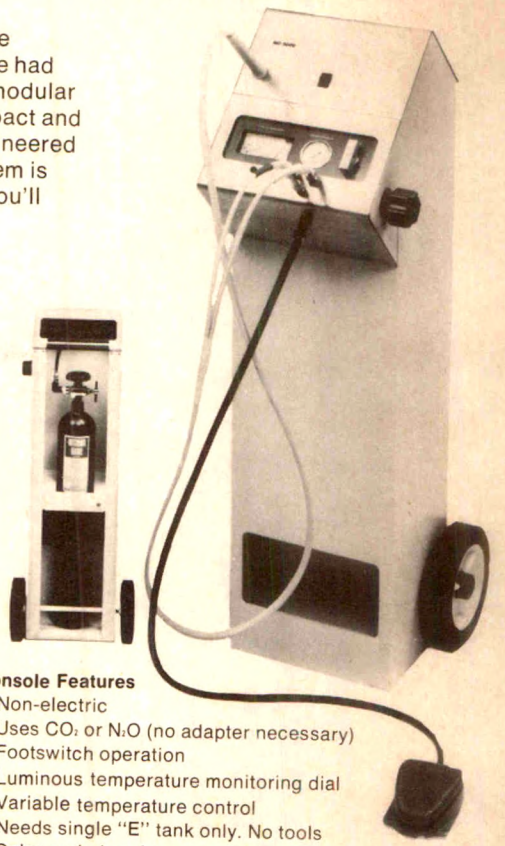
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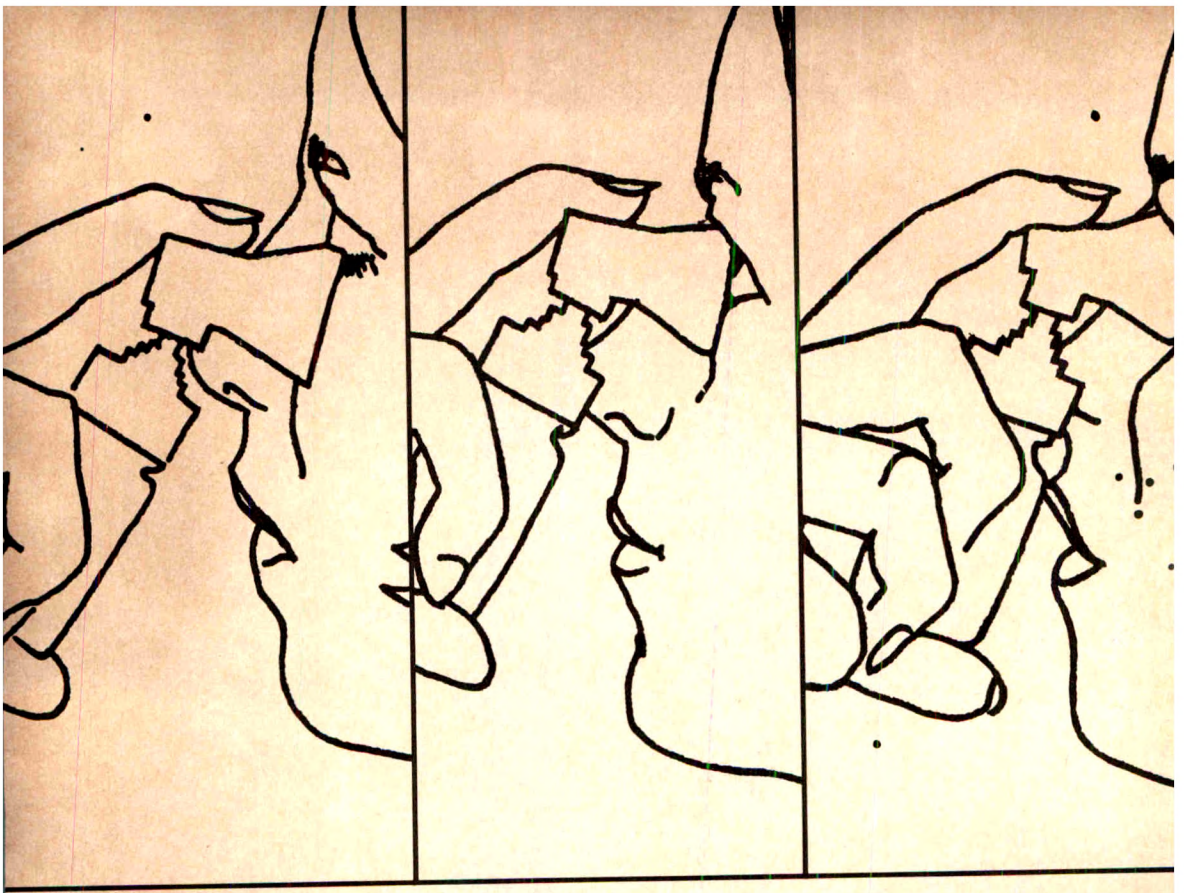
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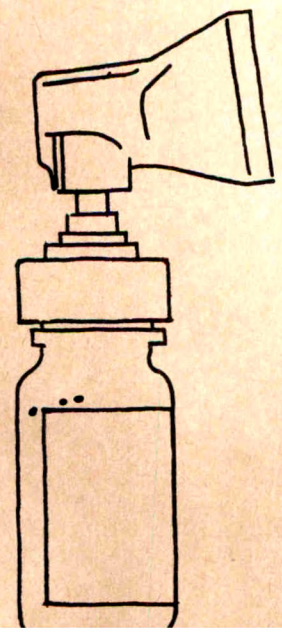
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Hold MISTURA between index finger and thumb. With the eye closed, place top rim of the lid-retractor (eyescope) just above eyelash of upper lid and use it to gently retract the eyelid.

Gently retract the lid. Be sure that the bottom of the eye-scope rests on the orbital bone. Look up within the eye-scope.

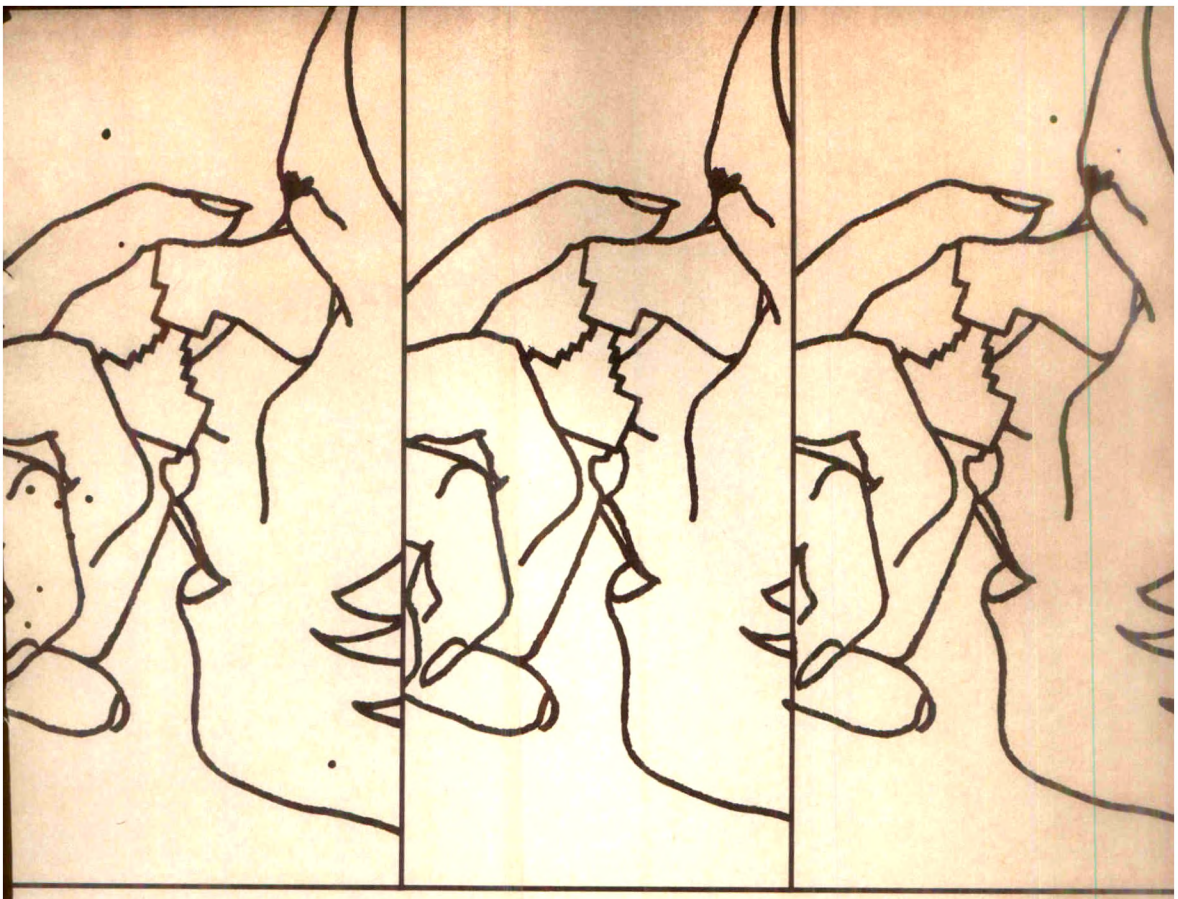
Briskly squeeze the thumb and index finger to deliver the medication as a fine mist of micro-drops.



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CONTAINS: Phenylephrine HCl 0.12% with: antipyrine 0.1%, sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium acetate, sodium thiosulfate, benzalkonium chloride 1:25,000 and purified water. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 6.75.
DIRECTIONS: Use 1 mist application in the affected eye(s). May be repeated in 3 or 4 hours as needed.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.
CAUTION: Should not be used in the presence of narrow-angle glaucoma.
WARNING: If irritation persists or increases, discontinue use. Keep container tightly closed.

NOTE: Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev.7/74

MISTURA® D.Zn

Phenylephrine with Zinc Sulfate

Ophthalmic Solution Sterile

DESCRIPTION: Zinc sulfate 0.25%, phenylephrine HCl 0.12% with: benzalkonium chloride (0.0075%), polysorbate 80, sodium bisulfite, sodium citrate, sodium chloride, (and purified water). Sodium hydroxide is added to adjust pH to approximately 6.9.
ACTIONS: MISTURA D.Zn phenylephrine with zinc sulfate is a mildly astringent solution of zinc sulfate and phenylephrine that provides prompt symptomatic relief of ocular irritation by whitening the inflamed eye and reducing mucus.
INDICATIONS: MISTURA D.Zn can be used when an astringent and decongestant is needed for relief of minor eye irritations such as those associated with hay fever, colds, dust, wind, sun, smoke, smog, swimming or hard contact lenses.
CONTRAINDICATIONS: MISTURA D.Zn should not be used in the presence of narrow-angle glaucoma.
WARNINGS: If irritation persists or increases, discontinue use and consult a physician.
DOSAGE and ADMINISTRATION: Use 1 mist application in the affected eye(s). May be repeated in three or four hours as needed.

When used according to accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA D.Zn.

NOTE: Keep container tightly closed. Not for use with the soft contact lens.

HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® C

Carbachol

Ophthalmic Solution Sterile

CONTAINS: Carbachol 0.75%, 1.5%, 3% with: benzalkonium chloride 1:20,000, disodium edetate, sodium chloride, potassium chloride and purified water. Hydrochloric acid or sodium hydroxide is added to adjust the pH to approximately 5.6.
ACTIONS: MISTURA C *carbachol* provides a more rapid and prolonged miosis than pilocarpine and can lower intraocular pressure when other miotics have had to be replaced due to irritation, insensitivity or insufficient potency.
INDICATIONS: Effective in reducing intraocular pressure in open-angle or narrow-angle glaucoma. Particularly useful in eyes which have become irritated by or resistant to pilocarpine.
CONTRAINDICATIONS: Carbachol is contraindicated in the presence of corneal abrasion and should never be administered orally or by injection. Miotics are contraindicated where pupillary constriction is undesirable such as in acute iritis.
PRECAUTIONS: Administer with caution if the epithelial barrier of the conjunctiva and cornea has been reduced by topical anesthetics, tonometry or trauma or if the patient is asthmatic. Headache and ciliary spasm with resultant temporary decrease in visual acuity may occur. Dosage must be individualized to avoid aching of the eye and frontal headache caused by constriction of the iris sphincter and ciliary muscle spasm.
DOSAGE and ADMINISTRATION: One mist application two to three times daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with MISTURA C available in three strengths.

When used according to the accompanying directions for use, each application delivers approximately 1.7 drops of MISTURA C.
HOW SUPPLIED: Available in sterile 15 ml. mist dispensing bottles. Rev. 7/74

MISTURA® E

1-epinephrine

Ophthalmic Solution Sterile

DESCRIPTION: Contains: levo-epinephrine (as the HCl) 0.25%, 0.5%, 1%, 2% w benzalkonium chloride, sodium metabisulfite, disodium edetate, sodium chloride, hydrochl acid qs ad pH approximately 3.0, and purified water.
ACTIONS: The capacity of MISTURA E *l-epinephrine* to decrease the aqueous inflo open-angle glaucoma has been well documented. Studies have also shown that prolon topical epinephrine therapy offers significant improvement in the coefficient of aqueous flow. (Becker[1] found that 55% of 72 patients showed a 50+% increase in outflow fac 6-24 months after initiation of topical epinephrine therapy.)

MISTURA E is effective alone in reducing intraocular pressure, and is particularly usef combination with miotics for the difficult-to-control patients. The addition of MISTURA the patient's regimen often provides better control of intraocular pressure than miotics (Ballentine and Garner[2] indicated that with 30% of the uncontrolled open-angle glaucom tients control might be expected with the addition of topical epinephrine therapy.)
INDICATIONS: Chronic simple glaucoma.
CONTRAINDICATIONS: Should not be used in patients who have had an attack of n angle glaucoma since dilation of the pupil may trigger an acute attack.
WARNINGS: Undesirable side reactions may include: eye pain or ache, browache, head conjunctival hyperemia and allergic lid reactions. Adrenochrome deposits in the conjun and cornea after prolonged epinephrine therapy have been reported. Epinephrine has be ported to produce macular edema in some aphakic patients and should be used with ca in these patients[3].
PRECAUTIONS: Epinephrine in any form is relatively uncomfortable upon instill However, discomfort lessens as the concentration of epinephrine decreases.

Should be used with caution in patients with a narrow angle since dilation of the pup trigger an acute attack of glaucoma.
DOSAGE and ADMINISTRATION: The usual dosage is 1 mist application once or twic However, the dosage should be adjusted to meet the needs of the individual patients. made easier with MISTURA E available in four strengths.

When used according to the accompanying directions for use, each application deliv proximately 1.7 drops of MISTURA E.

NOTE: Protect from excessive light and heat. If the solution discolors or a pre forms it should be discarded. Not for injection.
HOW SUPPLIED: 0.25%, 0.5%, 1% and 2% strengths available in 15 ml. mist dispensi tles.

REFERENCES

1. Becker, B., Pettit, T.H., and Gay, A.J.: Arch. Ophth. 66:219, 1961
2. Ballentine, E.J., and Garner, L.L.: Arch. Ophth. 66:314, 1961
3. Kolker, A.E., and Becker, B.: Arch. Ophth. 79:552, 1968 Rev. 7/74

MISTURA® P

Pilocarpine Hydrochloride

Ophthalmic Solution Sterile

CONTAINS: Pilocarpine HCl ½%, 1%, 2%, 3%, 4%, with: benzalkonium chloride 1:25,0 preservative sodium acetate, disodium edetate, sodium chloride, and purified water.
INDICATIONS: MISTURA P *pilocarpine HCl* is indicated for:

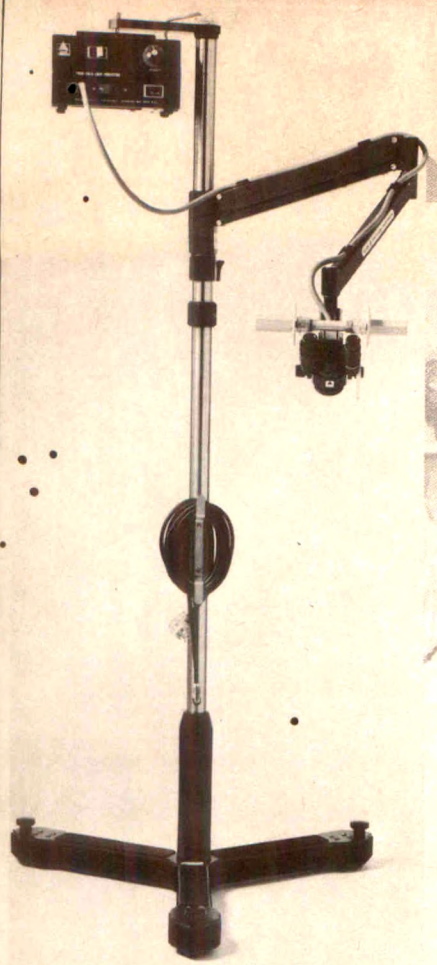
1. The control of intraocular pressure in glaucoma.
2. Emergency relief of mydriasis in an acutely glaucomatous situation.
3. Use following treatment with cycloplegics to reverse mydriasis.

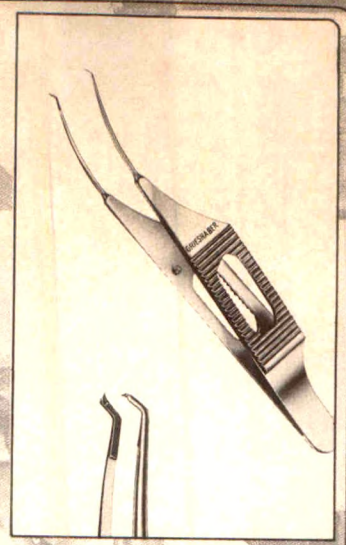
PRECAUTION: Undesirable side reactions to MISTURA P are rare; however, on p use, classic mucosal sensitization to pilocarpine may occur.
DOSAGE and ADMINISTRATION:

1. For glaucoma, the recommended dosage is 1 mist application two to four times the selected concentration; patient response may be variable.
2. To aid in emergency miosis, 1 mist application of the higher concentrations s used.
3. The dosage and strength required to reverse mydriasis depends on the cyclople

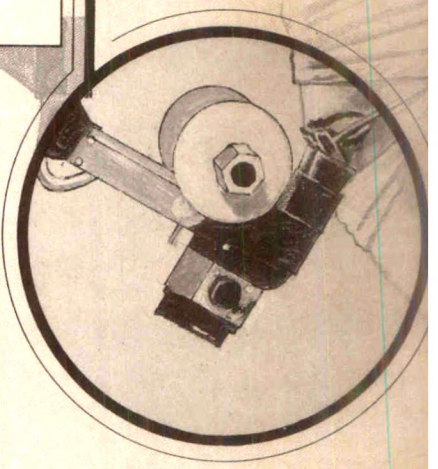
When used according to the accompanying directions for use, each application de proximately 1.7 drops of MISTURA P.
HOW SUPPLIED: MISTURA P *pilocarpine HCl* ½%, 1%, 2%, 3%, 4%, is available in ml. mist dispensing bottles. Rev. 7/74

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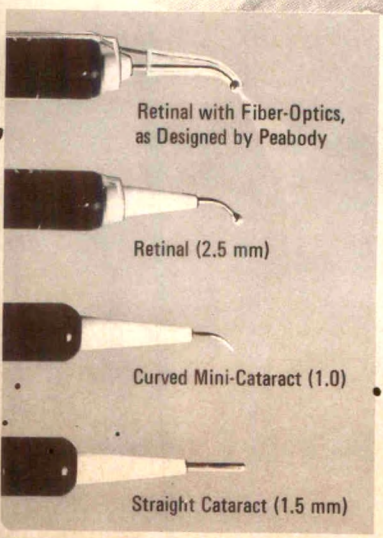
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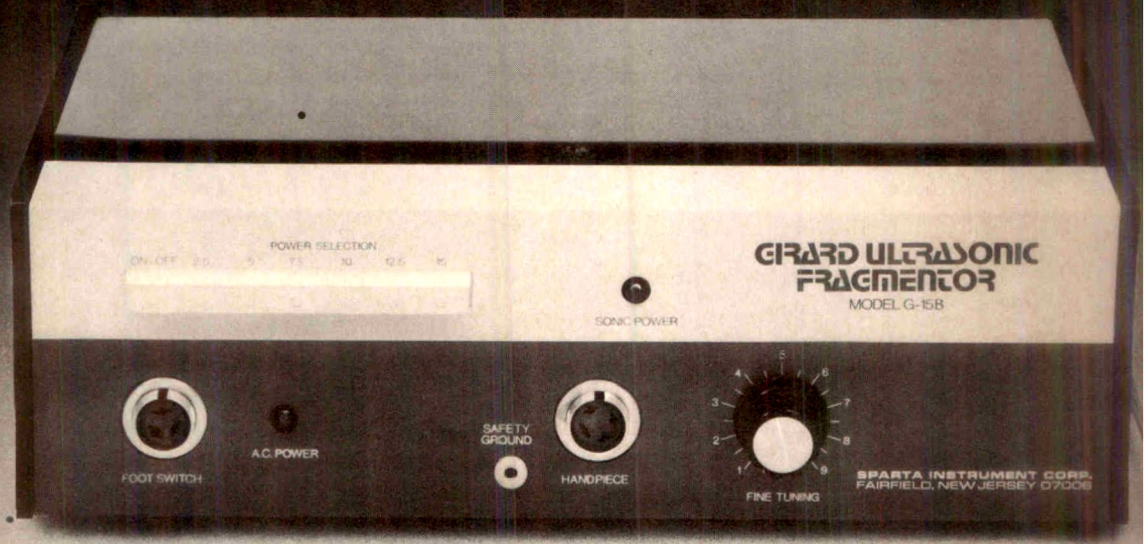
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*Louis J. Girard, M.D. and Rowland S. Hawkins, M.D., "Cataract Extraction by Ultrasonic Aspiration. Vitrectomy by Ultrasonic Aspiration". Transactions of the American Academy of Ophthalmology and Otolaryngology, Jan.-Feb., 1974, pp. OP-50-OP-59.

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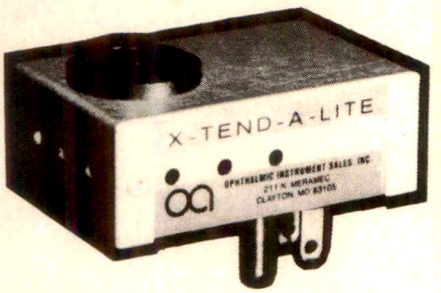
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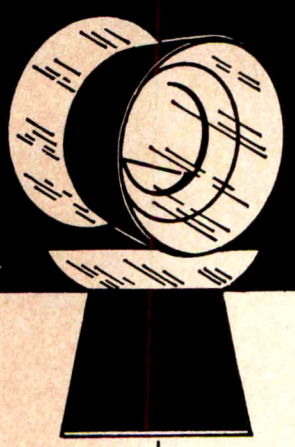
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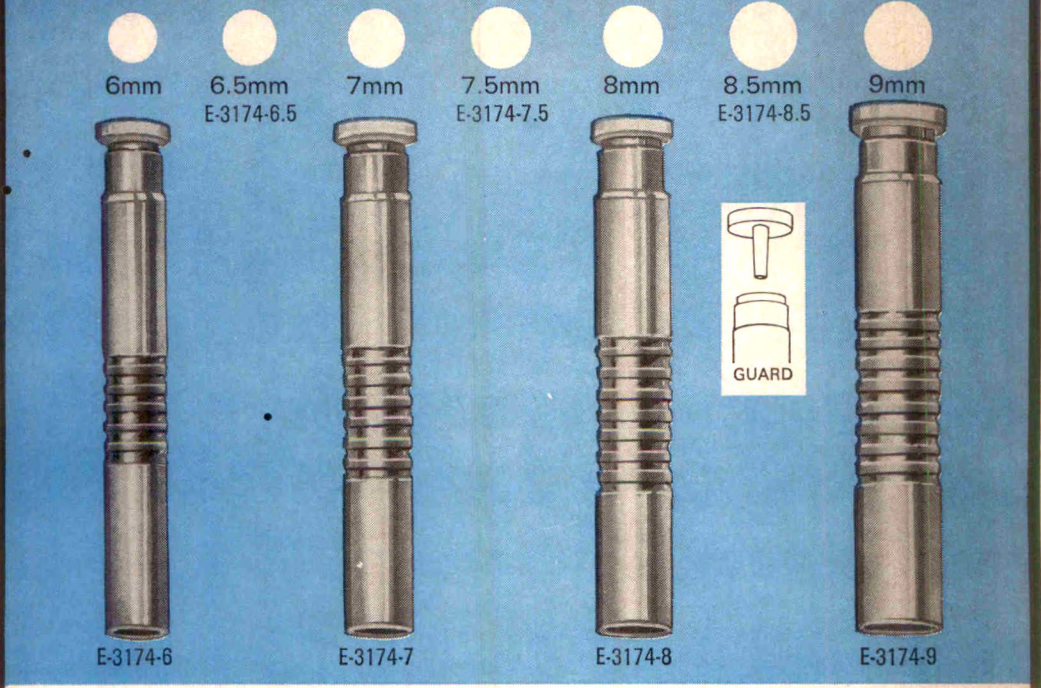
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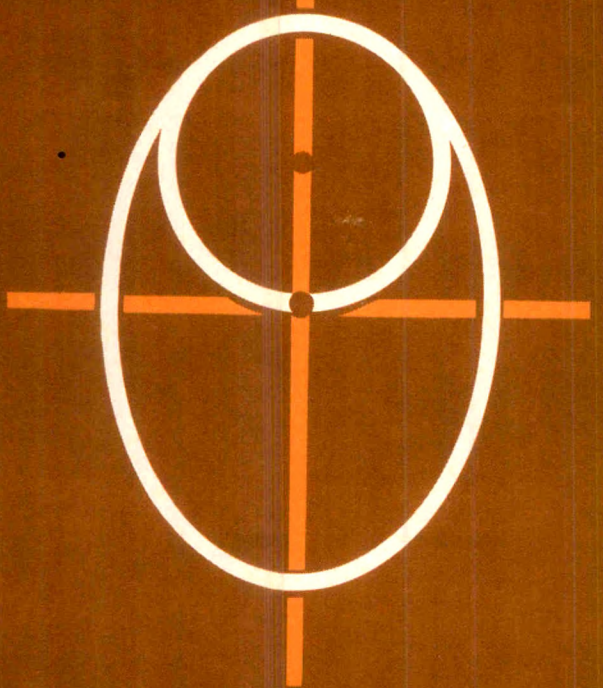
PRESERVING THE mm Hg

A COLUMN of fluid being kept up by the body's arterial system accords well with our conception of pressure and thus justifies the use of the millimetre of mercury in medicine. Gas tensions are recorded in the same units even though the column notion is less appropriate, and the pictorial analogy is pursued for central venous pressure even though 1 mm Hg and 1 cm water are of the same order of magnitude. Under the unified system of units known as SI there is only one unit of pressure, the pascal (Pa)*; and, since pressure can be defined in only one way, this unit or multiples of it should be as appropriate to people studying hypoxaemia or hypertension as it is to engineers, manufacturers of gas cylinders, or North Sea divers. This, anyway, is the theory. In practice the introduction of the SI pascal into clinical medicine is not going to be easy—and it may never happen. The formation of a Committee for the Preservation of the Millimetre of Mercury † suggests that clinicians are only just waking to the fact that SI involves them, and many and fierce have been the complaints about lack of proper consultations. In this respect the record of neither the Department of Health nor the profession has much to commend it: the Department chose a laboratory-oriented working-party to study the implications of SI for medicine, and the specialty bodies consulted do not seem to have taken the proposal seriously enough. But all that is past. The D.H.S.S. wants to see the kPa in the Health Service by December for blood-gas tensions. This means that oxygen from cylinders under pressures recorded in bar will be breathed in at pressures recorded in mm Hg and carried by the blood at tensions in kPa, and the recipient's blood-pressure will be monitored in mm Hg. This is not uniformity. The Department's reprieve of the column mm Hg and cm or mm H_2O is for two years, when the threat returns under an E.E.C. directive. The directive is not final, but the protest movement has only until October in which to plead for clemency. No country—E.E.C. or non-E.E.C., English-speaking or otherwise—shows any interest in, let alone enthusiasm for, change, and letters displayed in University College Hospital Medical School last week are ample evidence of the degree of support the committee can expect. In the laboratory the kPa is likely to win, but at the bedside it could well go the other way: those schooled in pascals will find the mm Hg easy enough to pick up, and it could be up to a new generation of doctors to decide on any future change. Those whose concern over SI extends beyond the sphygmomanometer will find no comfort in two items recorded *en passant* at last week's inaugural meeting. A case of diabetes has been tragically mismanaged because of confusion over molar units for blood-glucose: and representations in Brussels on the tricky problems of SI are in the hands of a Government Department which numbers among its concerns the price of fish fingers.

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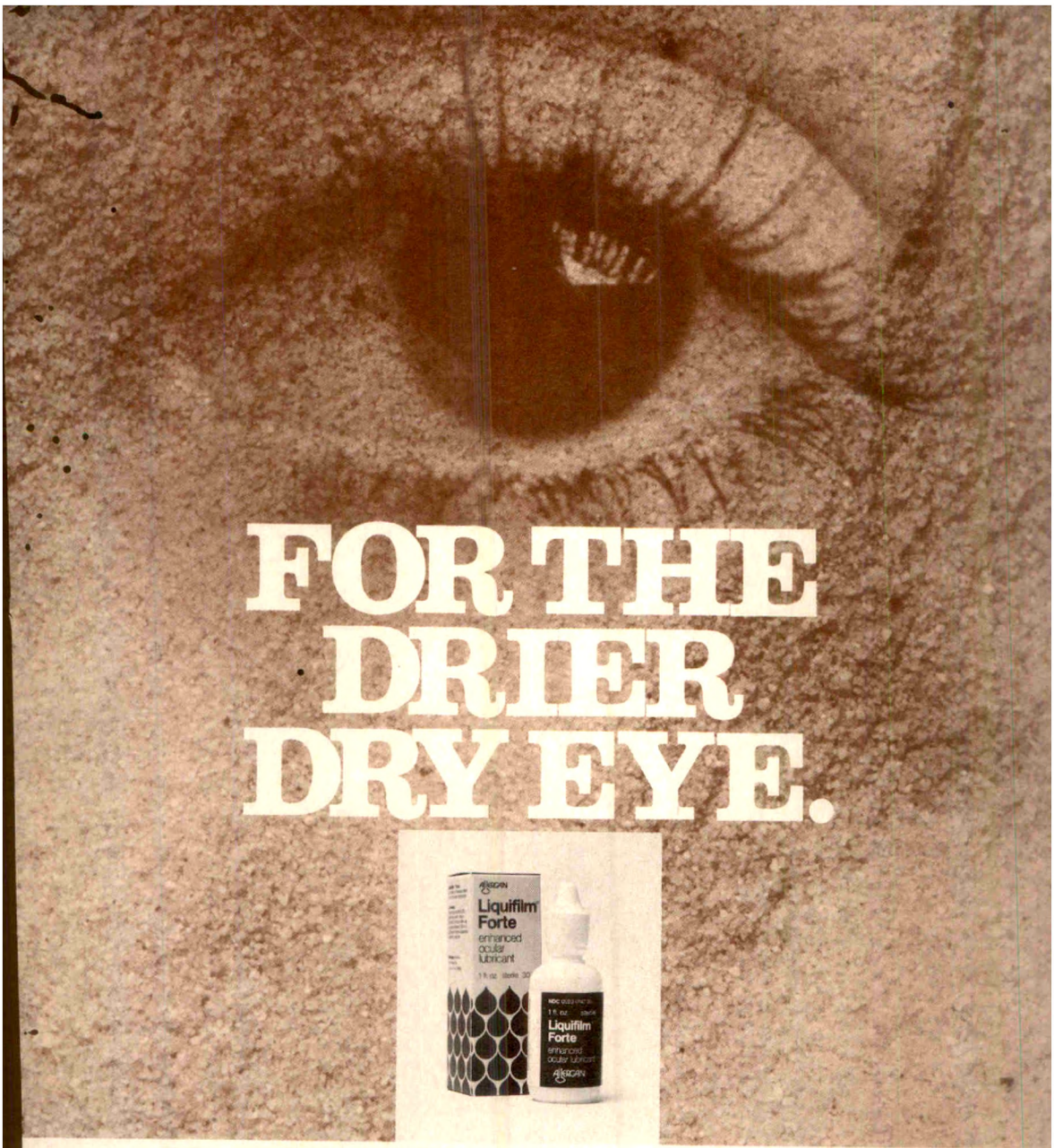
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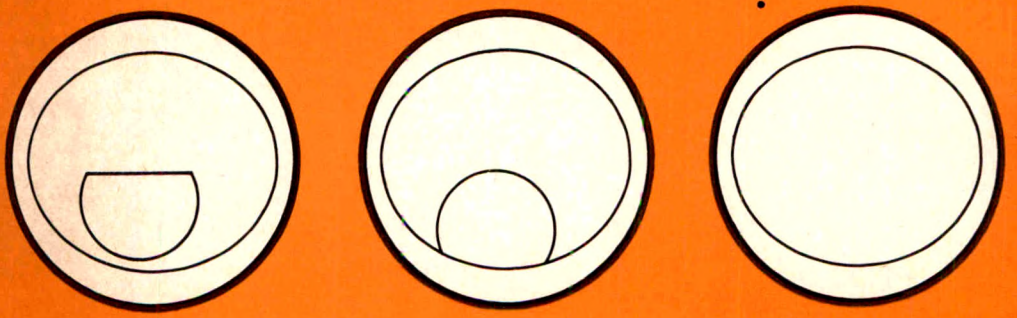
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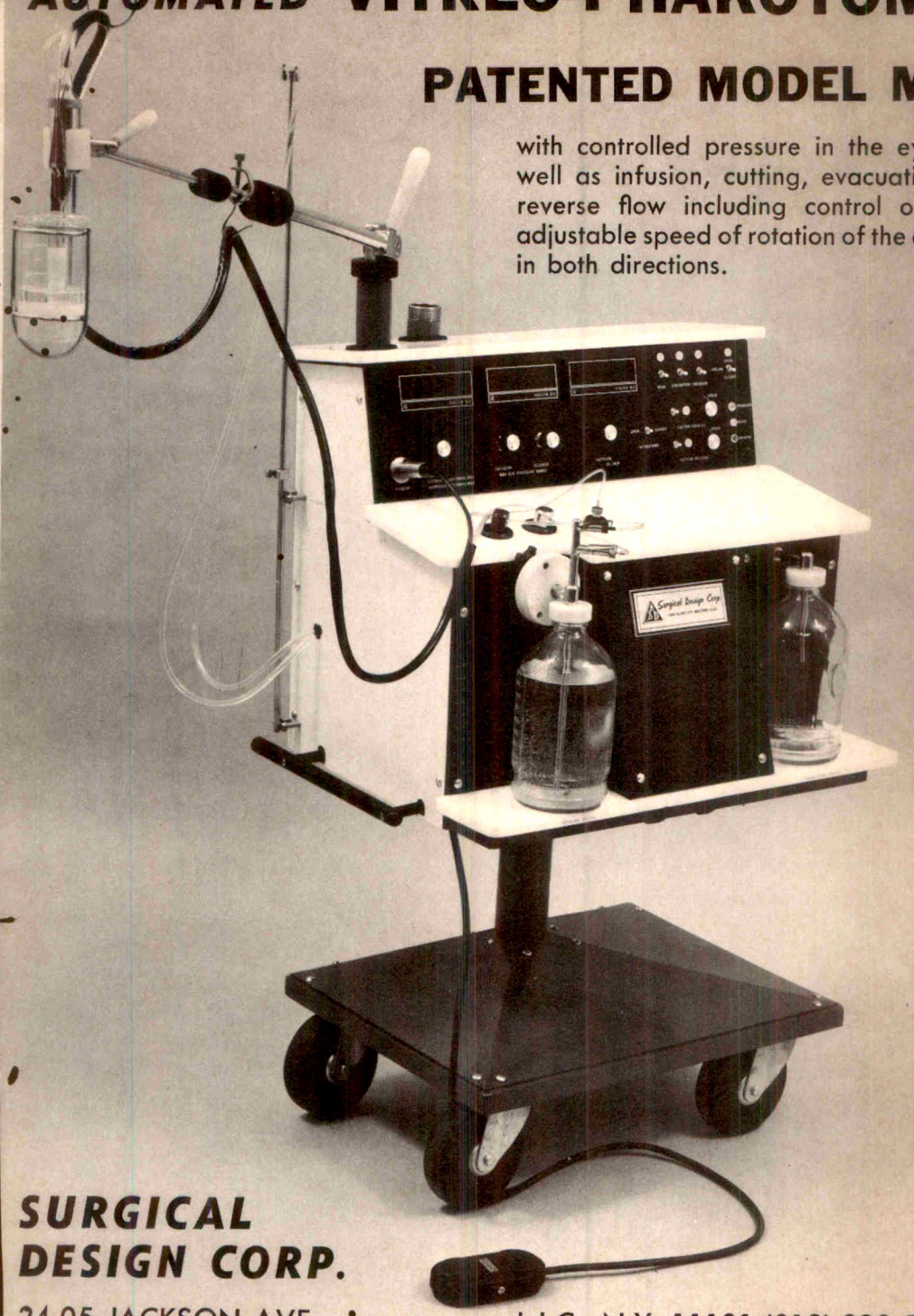
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1. Duke-Elder, S.: Diseases of the Outer Eye, Part I, System of Ophthalmology, Vol. VIII, The C. V. Mosby Co., (St. Louis), 1965, p. 68.

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 80 NOVEMBER, 1975 NUMBER 5

CORNEAL PRESERVATION USING M-K MEDIUM

JAMES V. AQUAVELLA, M.D.
Rochester, New York

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Wood, Wisconsin

AND

CECIL J. HAGGERTY, M.D.
Rochester, New York

For 15 years, as our knowledge of corneal physiology has expanded, several techniques have been proposed for the storage of donor corneal tissue. Yet, in most centers where corneal transplantation is routinely performed the methods of collection and storage of tissue have remained unchanged: the enucleated eye is stored in a moist chamber at 4°C up to 48 hours after the death of the donor.

In 1963, Stocker, Levenson, and Georgiade[1] reported favorable clinical results with many serum stored corneas. Several authors[2-4] have reported their experiences with the cryopreservation technique first described by Capella, Kaufman, and Robbins.[5] Although the current supply of donor corneal tissue is considerably less than the demand, and distribution of available material could be facilitated, the two described preservation techniques have not been widely accepted.

In 1974, McCarey and Kaufman[6] described a technique of preserving the corneal endothelium up to 14 days. We describe our experiences with the technique both in the laboratory and in 25 consecutive cases of penetrating keratoplasty.

MATERIAL AND METHODS

We employed the preservation medium described by McCarey and Kaufman[6] (M-K medium).* The 20-ml vials were stored at 4°C until needed. After the corneal tissue was placed in the vial 2,000 units of penicillin and streptomycin was added to the vial.

Flat preparations—Two pairs of eyes suitable for surgery were subjected to the following protocol. One eye was stored in the standard moist chamber at 4°C. The fellow cornea was excised with a small scleral rim, placed in the M-K preservation solution, and stored at 4°C. The paired tissue was removed four days after the death of the donor. The endothelium of each cornea was then stained with trypan blue and the results were recorded.

Electron microscopy studies—SERIES 1—

From the Departments of Ophthalmology and Physiology, Medical College of Wisconsin, and Research Service, Veterans Administration Center, Wood, Wisconsin (Dr. Van Horn); and the Rochester Eye Bank and Department of Ophthalmology, Park Ridge Hospital (Dr. Aquavella) and the Department of Ophthalmology, St. Mary's Hospital (Dr. Haggerty), Rochester, New York. This study was supported in part by Research grant 1974 Rochester Eye Bank (Dr. Aquavella), and grant EY00625, National Institutes of Health (Dr. Van Horn).

Reprint requests to James V. Aquavella, M.D., 1160 Chili Ave., Rochester, NY 14624.

* A mixture of TC-199 medium and 5% Dextran. The resultant solution has a pH of 7.4, PCO_2 at a maximum of 40, and osmolarity of 290 mOsm.

One cornea of a pair of eyes (24 hours after enucleation and unsuitable for keratoplasty) was excised and placed in the M-K medium for three, five, seven, 11, and 14 days. The fellow eye was stored at 4°C for the same period of time in standard conditions. Both corneas were then fixed with 2% glutaraldehyde before examination with a scanning electron microscope.

SERIES 2—One cornea of a freshly enucleated pair of young eyes was excised and placed in M-K medium for four days, while the fellow eye was placed at 4°C for the same period of time in standard conditions. Both corneas were then fixed as in Series 1.

SERIES 3—One of each pair of young surgically suitable corneas was stored for 48 hours or less in M-K medium before fixation. The fellow eye was stored for the same length of time under standard conditions.

Human keratoplasty—Human donor eyes were enucleated in routine fashion from 10- to 65-year-old donors. All enucleations occurred within six hours of death. The eyes were stored in a moist chamber at 4°C for 30 minutes to eight hours. The globes were immersed in neomycin polymyxin B sulfate (Neosporin) for five minutes before excision of the cornea with a 2-mm scleral rim. The donor tissue was placed in the vial containing M-K medium, 2,000 units of penicillin and streptomycin was added, and the corneas were stored at 4°C until surgery. All surgical procedures were completed between 68 and 80 hours after the death of the donor.

RESULTS

Vital staining of flat preparations—In one pair of eyes, the cornea that had been preserved in the M-K medium demonstrated more viable endothelial cells (unstained) than in the fellow cornea that had been stored under standard conditions in a moist chamber at 4°C. After four days of storage the cornea stored under standard conditions had more than 50% staining, while that stored in M-K medium had only 20% staining. In the second pair of eyes, both corneas had 50% staining after four days.

Electron microscopy—SERIES 1—This group consisted of tissue from three donors, aged 73, 79, and 80 years. Both eyes of a pair were stored under standard conditions for 24 hours after which one cornea was excised and placed in the M-K medium while the other cornea remained under standard conditions for three or five days (Figs. 1 and 2). The corneas stored in M-K medium demonstrated fewer endothelial degenerative changes than those stored under standard conditions. However, there was swelling of the mitochondria, cytoplasmic vacuoles, and the endothelial cells in the corneas preserved in M-K medium.

The other eyes in this series had been stored for seven to 14 days. This group of corneas (average patient age, 75 years) was stored under standard conditions for approximately 24 hours before being placed in the medium. In this group the corneas preserved under standard conditions and those subsequently placed in M-K medium demonstrated severe degenerative changes. Scanning electron microscopy (SEM) showed extensive folds in Descemet's membrane and many areas of dead cells. Transmission electron microscopy (TEM) showed dilated intercellular spaces and signs of cellular distress (edema, clefts, vacuoles, and swelling of mitochondria).

SERIES 2—One cornea of each pair of young freshly enucleated and surgically suitable corneas was stored at 4°C for four days. The fellow cornea was stored in M-K medium for four days. Scanning electron microscopy of the corneas stored in M-K medium for four days revealed many dead cells with exposed nuclei and mitochondria (Fig. 3). The fellow corneas stored under standard conditions demonstrated a greater percentage of lysed cells (Fig. 4).

The TEM studies of the specimens preserved in M-K medium revealed that the

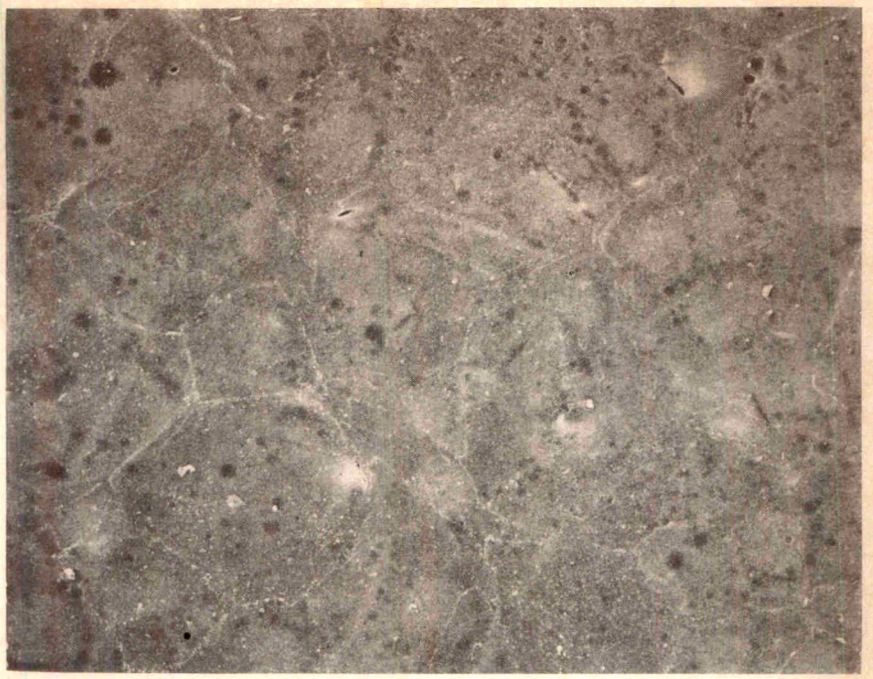


Fig. 1 (Aquavella, Van Horn, and Haggerty). Series 1 cornea preserved in M-K medium for five days. Endothelial mosaic-like pattern shows the presence of enlarged cells and surface pits (×1,000).

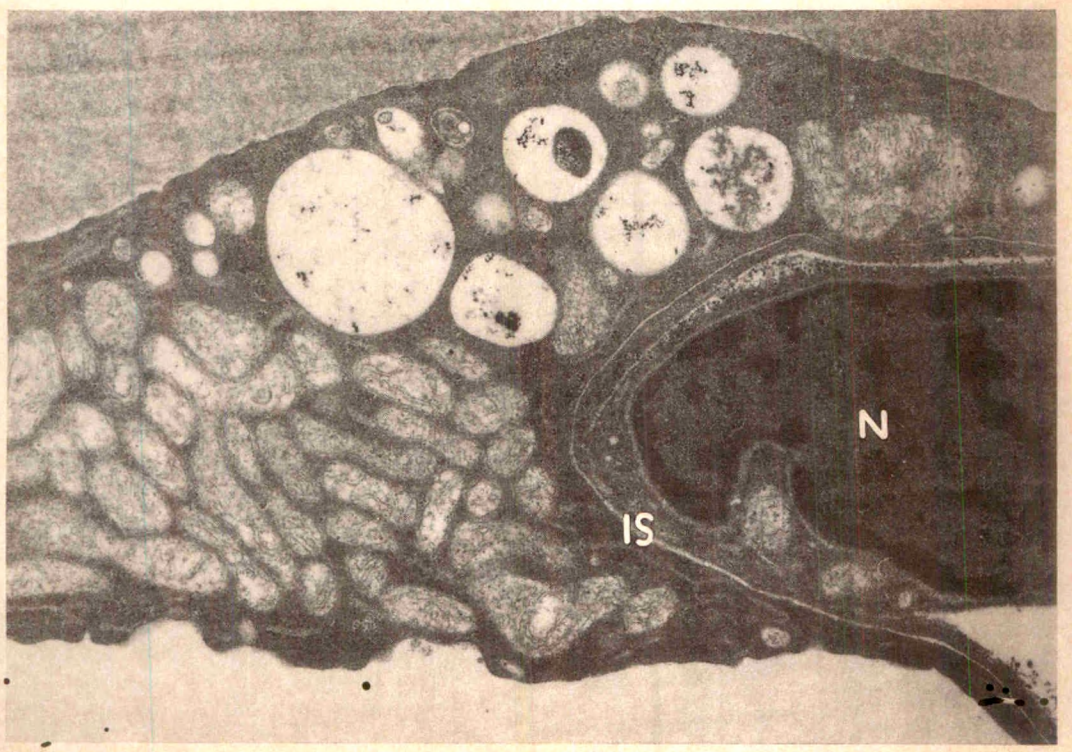


Fig. 2 (Aquavella, Van Horn, and Haggerty). Transmission electron microscopy of same specimen as in Figure 1. Note tight intercellular space (IS) and normal nucleus (N). Mitochondria are swollen and vacuoles and a cleft are present. The posterior surface is irregular (×19,500).

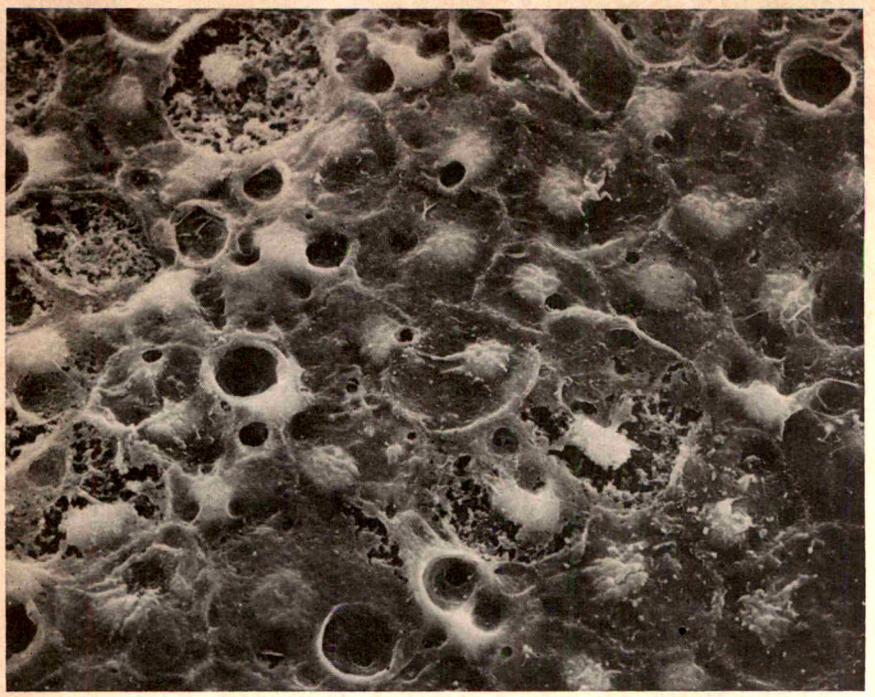


Fig. 3 (Aquavella, Van Horn, and Haggerty). Scanning electron microscopy of endothelium of a Series 2 human cornea stored in M-K medium for four days. The nuclei and mitochondria are exposed in those cells that have died. About one half of the cells still have intact posterior membranes (×1,000).

intact cells had pycnotic nuclei, swollen mitochondria, and irregular posterior surfaces (Fig. 5). The degree of cellular damage was greater in those corneas stored in a moist chamber (Fig. 6).

SERIES 3—The young surgically suitable corneas stored in M-K medium for 48 hours or less demonstrated normal ultrastructural patterns on both transmission and scanning electron microscopy (Figs. 7 and 8).

Clinical keratoplasty—In June 1974, 25 consecutive penetrating keratoplasties were performed with tissue preserved in M-K medium (Tables 1 and 2). In all 25 cases the donor tissue was crystal clear from the first day. There were no primary graft failures. Twenty-three grafts were clear and no grafts have opacified. Two were moderately clear and in one of these a delayed graft rejection occurred 415 days postoperatively. Although the condition seems to have been reversed, we elected to place this case in the questionable category.

We observed all of the grafts for at least 90 days. Corneal thickness was measured periodically. Nine and ten weeks after the operations, the average thickness of the transplanted corneas was 0.47 mm. Only one cornea was thicker than 0.58 mm.

DISCUSSION

In analyzing the results of the vital staining and Series 1 electron microscopy corneas, we conclude that although the condition of the corneas preserved in M-K medium is superior to those stored under standard conditions, the endothelium in the corneas preserved in M-K medium was not as good as one would prefer. There are several possible reasons for this. The experimental corneas were not placed in M-K medium as soon as the eyes were enucleated; the donor patients were old; and the corneas were kept at refrigerator temperature before fixation, inhibiting the metabolic processes. Because of these find-

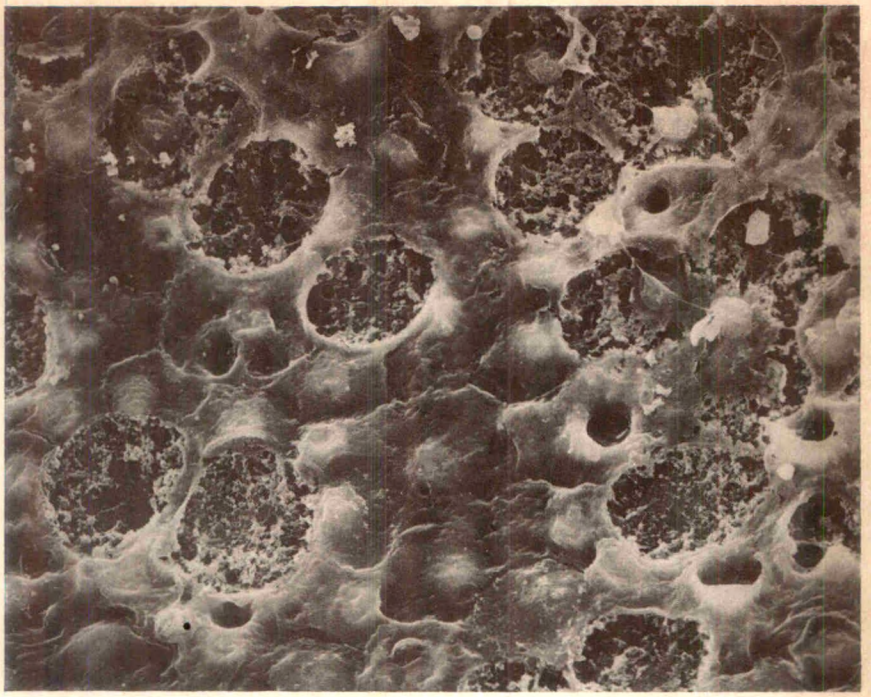


Fig. 4 (Aquavella, Van Horn, and Haggerty). Scanning electron microscopy of endothelium of fellow cornea (Fig. 3) stored in refrigerated moist chamber for four days. More cells have died and broken open (×1,000).

ings we used only corneas from young donors and the tissue was placed in M-K medium immediately after enucleation.

Scanning electron microscopy enables one to see all the endothelial cells on one half of the corneal surface and thus affords the opportunity to provide quantitative data. Extensive changes may, of course, take place before the posterior cell membrane is involved; however, there was a good correlation between our results with vital staining and SEM.

Most human corneas available for laboratory study are not suitable for transplantation because of the age of the donor or the length of time elapsed after the death of the donor. Thus, when attempting to compare the results of different series, even those



Fig. 5 (Aquavella, Van Horn, and Haggerty). Transmission electron microscopy of intact endothelial cells in same cornea as in Figure 3. Nucleus (N) is pycnotic, mitochondria are swollen, and posterior corneal surface is irregular due to absence of a cell (×8,000).

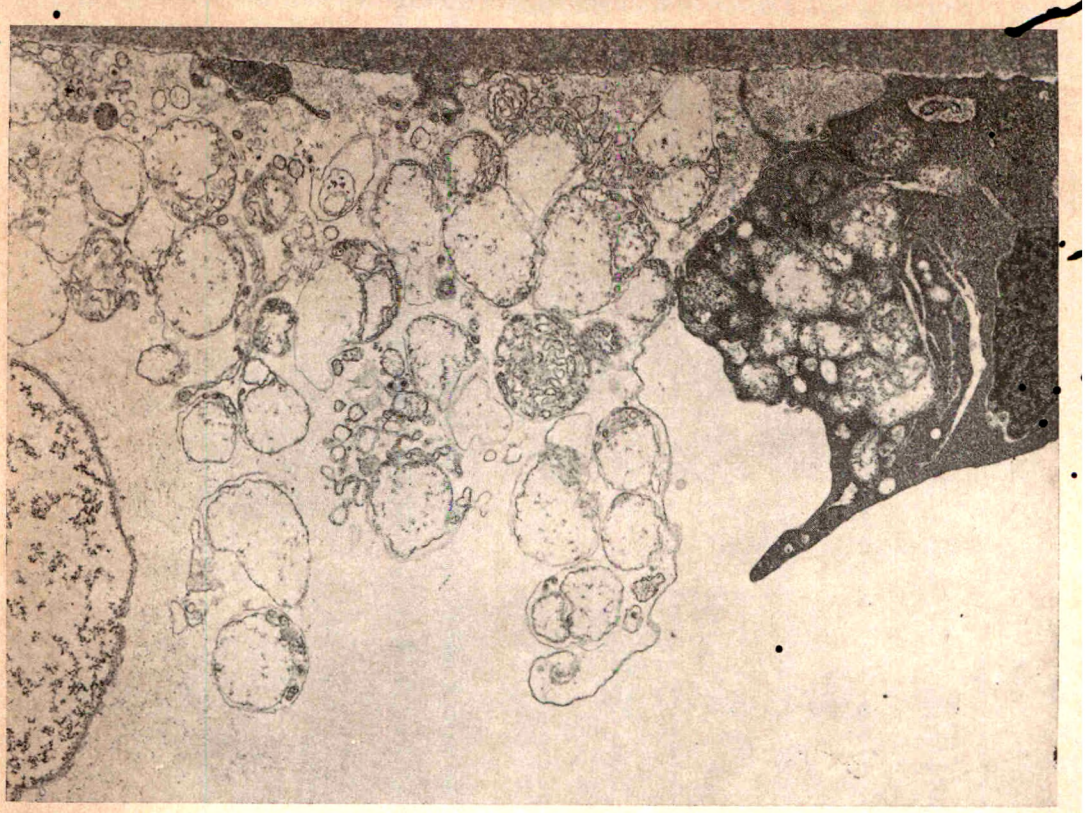


Fig. 6 (Aquavella, Van Horn, and Haggerty). Transmission electron microscopy of disrupted cell with swollen nucleus and mitochondria in same cornea as in Figure 4. An intact cell is at right (×10,000).

performed by the same investigator, it is essential to be fully aware of these factors as well as the specific environments the donor tissue was subjected to before fixation. The M-K medium is designed to preserve viable surgical corneas and the limits of this procedure must therefore be explored utilizing human tissue. Nevertheless, in this study those corneas maintained in M-K medium for seven days and longer demonstrated severe, probably irreversible, morphologic changes when examined with scanning and transmission electron microscopy.

An important concept is that of the "aqueous sewer."[6,7] One must be conscious of the length of time that the donor endothelium has remained in contact with the aqueous humor in the enucleated eye. The cornea should be removed from the enucleated eye where it is in contact with the postmortem aqueous humor and placed in the M-K medium as soon as possible after the death of the donor. The endothelium may be maintained in excellent condition in M-K medium for 48 hours or less. However, our study produced no definite morphologic evidence that storage in M-K medium is superior to moist chamber storage within 48 hours of enucleation (Figs. 7 and 8).

The major drawbacks to the cryogenic preservation system are the necessity of preserving tissue within a short period after the death of the donor (six hours), the relatively expensive equipment required, and the complexity of the controlled freezing and thawing process. A great advantage of the M-K storage technique is that enucleation and storage may commence in a routine fashion, eliminating the necessity for a trained technician on 24-hour call. This is

rticularly important in eye banks that serve several hospitals and those in semi-rural areas. It requires more than a modicum of diligence to insure that the basics of timely enucleation, proper moist chamber storage, adequate refrigeration, and speedy transportation are carried out. The additional requirement of immediate excision of the cornea by relatively untrained personnel is unwise.

In addition, the mechanics of the M-K procedure are more simple than those of cryopreservation. The vials of medium may be stored at 4°C for at least one year. It is preferable to maintain the penicillin and streptomycin in a frozen state, but it quickly thaws before use.

The removal of the cornea with a scleral rim continues to be a critical step in the process. Ideally, whether transplantation is suitable is determined by slit-lamp microscopy before removal of the cornea and storage in the M-K medium. If the anterior chamber is lost before excision of the cornea, endothelium must be regarded as having been compromised and the cornea should not be used for transplantation.

Conceivably, tissue stored in M-K medium may be subsequently cryopreserved without irreversible endothelium damage. This insures a supply of viable corneas for emergency use. The intermediate and long-term preservation systems should complement each other and must not be assumed to be mutually exclusive.

We hope that the maximum storage time for the present M-K procedure is expanded. With clinical keratoplasty we hope to extend the present limit to 100 hours. Practically, five- to seven-day-old tissue may be adequate for the needs of most eye banks. The results of our investigation do not justify expansion of the current limits beyond 96 hours although McCarey and Kaufman[6] reported that M-K preserved rabbit corneas (using direct observation with the specular microscope and temperature reversal) were viable up to 14 days. Our studies, however, re-

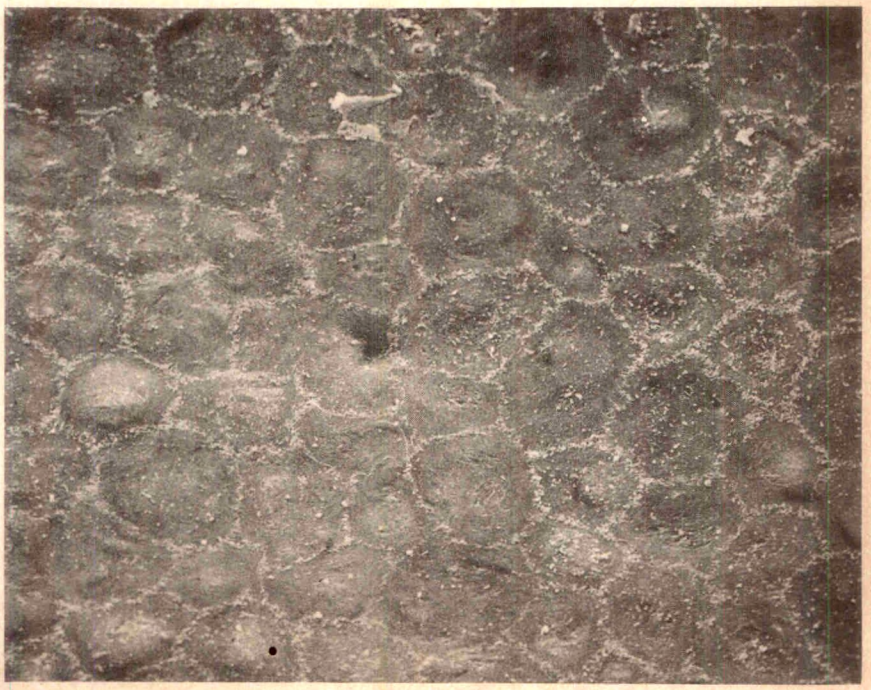


Fig. 7 (Aquavella, Van Horn, and Haggerty). Series 2 cornea preserved in M-K medium for 36 hours. Normal mosaic-like pattern of hexagonal endothelial cells is present (×1,000).

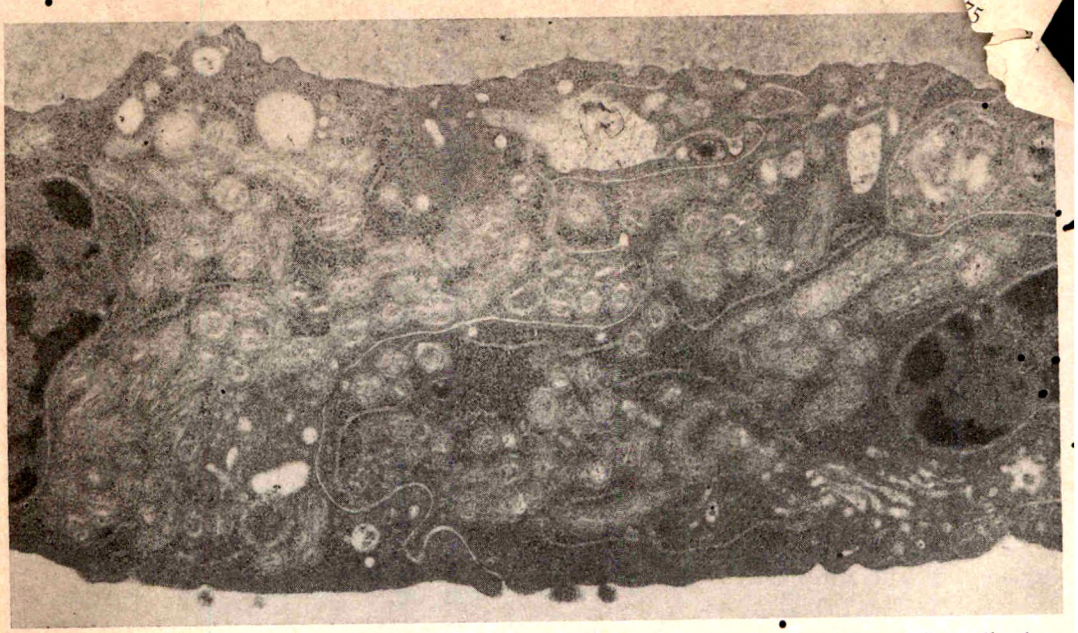


Fig. 8 (Aquavella, Van Horn, and Haggerty). Same specimen as in Figure 7. Endothelial cells show vacuolization (×16,200).

vealed significant endothelial damage after four days that may represent another example of the inherent differences that exist between the rabbit and human endothelium.

Our preliminary results are encouraging, although we need more time to evaluate completely the clinical results. This series comprised a variety of clinical diagnoses and over 55% of the surgical procedures were in aphakic eyes or were combined with lens extraction (Tables 3 and 4). The corneal thickness measurements we observed in this study correlate well with corneal thickness patterns previously reported for both refrigerated and cryopreserved corneas.[8,9]

The percentage of clear grafts in this series was 92%. This is considerably better than the 77% success ratio reported in a similar series of 48 cases where cryopre-

TABLE 1

CURRENT STATUS OF DONOR TISSUE PRESERVED IN M-K MEDIUM

	No. of Grafts	
Clear	23	
Moderate	2	(1 delayed rejection)
Opaque	0	
Total	25	

TABLE 2

POSTOPERATIVE GRAFT CLARITY

Postoperative Days	No. of Grafts
90–120	12
121–150	4
180–210	9
Total	25

TABLE 3

PRIMARY INDICATION FOR KERATOPLASTY

Herpes simplex keratitis (inactive)	1
Herpes (active)	2
Chemical keratitis	1
Leukoma (adherent)	3
Ulceration	1
Keratoconus	4
Bullous keratopathy	9
Fuchs' dystrophy	3
Anterior membrane dystrophy	1
Total	25

TABLE 4

TYPE OF SURGICAL PROCEDURE

Primary	19
Regraft	6
Total	25
Simple	11
Aphakic	10
Combined	4
Total	25

served corneas were utilized.[4] The higher success rate may be related to the fact that the present study is smaller and contains more keratoconus and other primary grafts. However, the storage time in M-K medium was limited to between 68 and 80 hours in the present study.

SUMMARY

Human eye bank corneas were preserved in M-K medium for varying periods of time after which viability of the endothelial cells was evaluated by vital staining and scanning and transmission electron microscopy. Endothelial viability and ultrastructural integrity was maintained in some corneas up to four days. Twenty-five consecutive keratoplasties were performed utilizing human donor material stored in M-K medium. There were clear grafts in 92% of the cases and there were no primary graft failures. After the ninth postoperative week, the average central corneal thickness was 0.47 mm and 23 of the 25 grafts remained clear to moderately clear. All of the donor material used for keratoplasty was stored in M-K medium for less than 80 hours.

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ENDOGENOUS *CANDIDA* ENDOPHTHALMITIS LEADING TO BILATERAL CORNEAL PERFORATION

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Since the first histopathologic report of endogenous *Candida* endophthalmitis in 1943[1] and the first clinical description of a case in 1958,[2] numerous case reports followed. In 1970 11 new cases were reported.[3] This case, to our knowledge, is the first reported in a neonate and represents a most unusual, fulminant course of infection in the eyes. *Candida* endophthalmitis represents a potentially curable entity, early recognition and institution of therapy being the most important factors determining success in saving vision and often life.[3] It is thus important to suspect any endogenous ocular infection or recalcitrant inflammation, especially in the clinical setting predisposing to blood-borne *Candida* organisms.

CASE REPORT

This 1,680-g boy was born to a 14-year-old gravida 1 para 0 mother whose pregnancy had been complicated by one episode of readily resolved pyelonephritis from *Escherichia coli*. After spontaneous controlled vaginal delivery an Apgar rating of 5 was assigned to this infant who had slow respirations. He was given oxygen for five minutes, after which he responded well. At 2 days of age, however, he had an acute episode of apnea and cyanosis and was noted to have many ecchymotic lesions over his back and abdomen. Blood glucose level was less than 40 mg/100 ml. He was evaluated for sepsis and begun on systemic kanamycin, penicillin, and glucose. At 4 days of age, because of an increasing bilirubin, he had an exchange transfusion. At 9 days of age, 10 mg/day of hydrocortisone was added as the blood glucose was recorded at 25 mg/100 ml. At 22 days of age he spiked a temperature of 105° F and a urine culture was reported positive for *Klebsiella*. Colistin sulfate (Colymycin) was then substituted for kanamycin as a result of bacterial sensitivity studies. On the 26th day of life bilateral opacities in the pupillary areas of the anterior chamber were noted. An ophthalmologic consultation revealed bilateral hypopyons in the pupillary areas and a central descemetocele in the left eye. The corneas, however, were clear. A mucoid conjunctival discharge was present but was negative for organisms on both microscopic examination and culture. Two days later the hypopyon of the right eye had progressed and filled the anterior chamber while the left cornea had perforated (Figs. 1-3). Bilateral metastatic *Candida* endophthalmitis was suspected after review of the patient's record revealed positive cultures for *C. albicans* and *Klebsiella* at 9 days of age from the area of the catheterized umbilical vein, and at 18 days of age for *Candida* alone from the blood. Subsequently, at 28 days of age a suprapubic tap of urine and, at 32 days of age, an intravenous catheter tip were positive for *Candida* alone. The exudate from the perforated left eye was examined and cultured and reported as *Candida* only.

Intravenous amphotericin B, 2 mg/day, and orally administered nystatin, 100,000 units four times daily, were begun on the 27th day. The patient was also started on 0.5% atropine drops three times daily and amphotericin B solution (1 mg/ml) drops every hour bilaterally. After two days the nystatin (given by nasogastric tube) was discontinued. Within 48 hours after the left eye had perforated, the right cornea thinned centrally and pointed (Fig. 4) and then perforated (Fig. 5). It appeared to be extruding the lens through the perforation, but an identifiable specimen could not be obtained. Over the next few days the chambers remained flat but free of exudate. The infant exhibited a response to bright light in the right eye but not in the left. His general condition remained precarious; an anemia with a hematocrit reading of 24% required a transfusion of 40 ml of whole blood on the 42nd day of life. On the 45th day the patient's creatinine level had risen to 4.1 mg/100 ml. The amphotericin B was then discontinued after a total dose of 36 mg. The infant developed increasing symptoms and signs of massive pneumonitis, however, and died on the 49th day of life despite the institution of methicillin and kanamycin therapy.

RESULTS

Postmortem examination revealed *C. albicans* sepsis with identifiable organisms in foci of infection located in the lungs, kidneys, and brain where some white plaques were found lining the ventricles.

Histopathologic examination revealed a healing corneal perforation in the right eye with adherent lens remnants, vitreous inflammation and condensations, and some foci

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Fig. 1 (Michelson, Rupp, and Efthimiadis). Hypopyon of right eye and recently perforated left descemetocele after rapidly expanding hypopyon and "pointing" of cornea.

of retinal necrosis. Some budding yeast forms were identified in the adhesions of lens remnants and iris to cornea and in the posterior chamber, but not in the retinal foci. The left eye had similar findings, but contained an anterior focus of choroidal necrosis underlying retinal and vitreous inflammation. Some slightly distorted pseudohyphae were identified with the Grocott-methenamine silver stain in the anterior vitreous, but not in the disorganized anterior chamber, cornea, or focus of choroidal and retinal necrosis.

Discussion

As expected with a septic process, foci of organisms can lodge randomly throughout the body. While the most common clinical ocular findings involve the retina, choroid, and vitreous body,[3,4] foci of infection have been found in the cornea[5] and histopathologically in the ciliary body[3] as well. Smelianski[6] reported a case of endogenous *Candida* endophthalmitis presumably limited to the anterior chamber. Both eyes in the case reported here had additional foci of infection posteriorly in the choroid or retina, or both. While no organisms were demonstrable in these lesions, it has been shown that the retinal and choroidal foci are most amenable to amphotericin therapy.[3,4] When untreated, choroidal and retinal lesions progress to vitreous involvement with endophthalmitis. Organisms within the vitreous body are then at best slowly responsive.

Most reported cases have occurred in individuals who are hospitalized and undergoing intravenous therapy. One report on *Candida* sepsis suggests direct inoculation by intravenous catheters is the most common source of blood-borne infection[7]; another series[4] reported six out of six patients had positive cultures of *Candida* from the intravenous catheter tips. A significant number of similar cases were noted in our series in 1970.[3] Other foci of asymptomatic *Candida* growth or clinical infection such as the skin, genitourinary and respiratory tracts were also noted and discussed, however. These sites may have seeded the blood as well, as not all of the patients had had intravenous therapy. Most intriguing were two patients who exhibited clinically no systemic disease or other organ involvement.[3]

Factors seemingly predisposing to *Candida* sepsis are exemplified by the case presented here. Most common is a history of prolonged broad-spectrum antibiotic therapy. While corticosteroids and immunosuppressives must be considered predisposing factors as well, only about one half or fewer of the patients described have received these agents. About one third had underlying diseases such as diabetes or blood dyscrasias that might affect immunologic competence, while about one fourth were

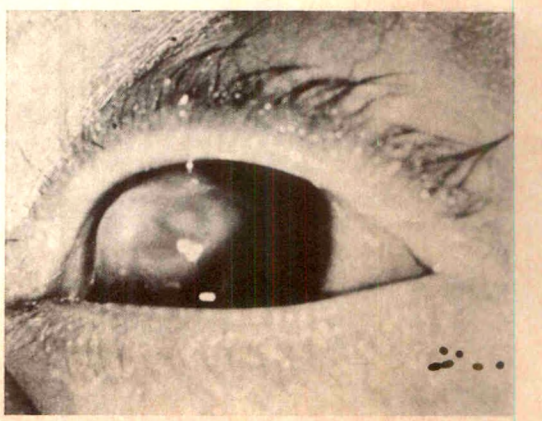


Fig. 2 (Michelson, Rupp, and Efthimiadis). Left eye after perforation of cornea, extrusion of purulent material, and flattening of anterior chamber.

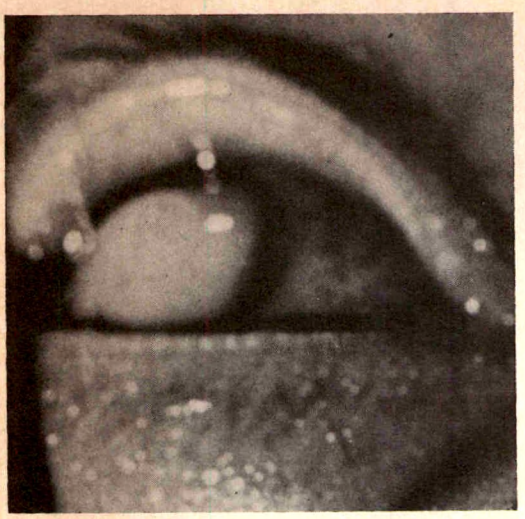


Fig. 3 (Michelson, Rupp, and Efthimiadis). Right eye with rapidly expanding hypopyon.

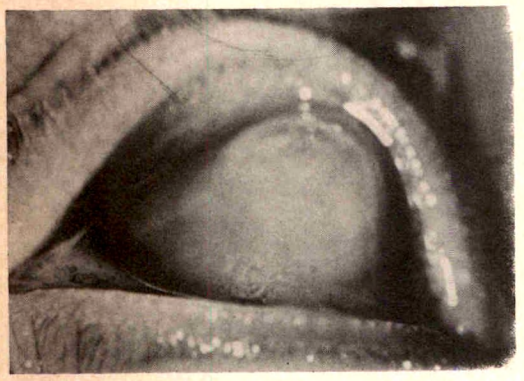


Fig. 4 (Michelson, Rupp, and Efthimiadis). Right eye 24 hours after Figure 3.

in a moribund state. Almost all patients had received antibiotics, however. Many hospitalized patients had had intravenous therapy.[3,4]

The most characteristic lesion of ocular candidiasis is a fluffy white inner retinal lesion actually resembling a fungal colony on culture media. The overlying vitreous body is turbid with inflammatory cells. As the infection progresses, small discrete fluff balls with a surrounding halo of inflammatory cells develop in the vitreous body. Earlier, however, nonspecific choroidal lesions, deep retinal lesions, hemorrhages, and Roth spots may occur.[3] Later, a fully developed endophthalmitis may present, as in our case with bilateral hypopyons. Approximately one half of the cases in one series had bilateral involvement.[3] The dramatic and rapid progression in the present case was probably due to the advanced state of the endophthalmitis when first detected, the poor immunologic response of this premature infant, and the immature state of the corneas. Diagnosis of endogenous *Candida* endophthalmitis is usually made from the clinical setting and the history of positive blood cultures. Suspicion should also be aroused, however, if *Candida* is cultured from other areas, either asymptomatic or clinically infected. Several cases have been diagnosed clinically by anterior chamber taps[6,8] and one case by a vitreous aspiration through the pars plana.[3] Treatment affords excellent chance of recovery if the infection is diagnosed early; some relatively advanced cases have responded well also.[3,9] Amphotericin B in appropriate dosage has been the most uniformly effective,[3,4] but it has several adverse side effects, the most significant of which is renal toxicity. Nystatin is of no benefit for systemic infection as it is not absorbed from the gastrointestinal tract, but it can eradicate foci of potential infection in the mouth and intestine if such exist. More recently flucytosine has been introduced and found to

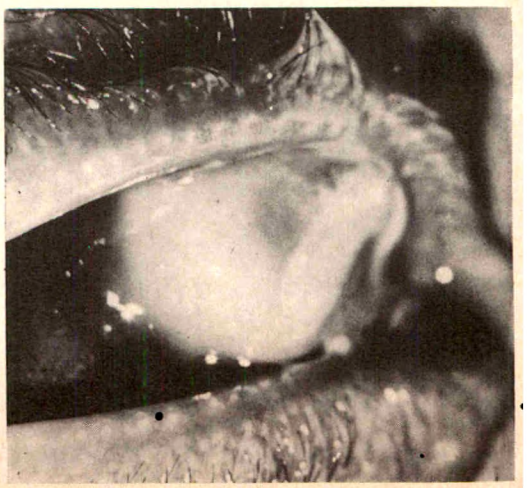


Fig. 5 (Michelson, Rupp, and Efthimiadis). Right eye after perforation of cornea and extrusion of some purulent intraocular contents.

be effective against some but not all strains of *Candida*.[10-12] Sensitivity studies are thus indicated if treatment is to be considered with this agent. One ocular case has been reported which apparently did not respond to flucytosine, but did respond subsequently to amphotericin.[9] If the organism is sensitive, however, flucytosine appears to be a less toxic and more easily administered agent than amphotericin B, and success in treating ocular infection with it has been reported.[8] Systemic therapy is mandatory in these cases as the ocular infection is almost always part of a generalized sepsis involving other organs as well. In a series of postmortem cases, Griffin and associates[4] found that 13 of 15 patients with eye lesions had at least one other organ involved, while Green found that of 16 patients diagnosed at autopsy as having had *Candida* sepsis, six had ocular lesions (personal communication). Thus the eyes are not necessarily a site of predilection for *Candida* infection and must be considered indicative of a generalized and life-threatening process when involved. Certainly ocular examination, preferably with dilation and indirect ophthalmoscopy, seems indicated in any patient with positive *Candida* cultures from blood or catheter tip. A guide to the significance of such positive cultures, often ignored as either contaminations or indicative of a "harmless candidemia," can thus be obtained.

Summary

A premature neonate developed advanced bilateral endophthalmitis before the significance of underlying *Candida* sepsis was appreciated. Severe endophthalmitis resulted in corneal thinning, descemetocele formation, and perforation. The infection occurred in the clinical setting of broad-spectrum antibiotic therapy and indwelling intravenous catheters. Cultures of blood and catheter tips had been positive for *Candida* but were not considered significant until advanced ocular infection was noted. The septic process resulted in the infant's death after systemic amphotericin B therapy was discontinued because of renal toxicity.

Acknowledgments

We thank W. Richard Green, M.D., and Donald Nicholson, M.D., of the Eye Pathology Laboratory, Johns Hopkins Hospital, for the histopathologic evaluation of the right eye.

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EXOGENOUS CORNEAL ULCER CAUSED BY *TRITIRACHIUM ROSEUM*

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AND

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In recent years, saprophytic fungi have been implicated with greater frequency in corneal mycotic infections.[1,2] *Tritirachium roseum* has not been previously associated with human exogenous or endogenous infection. To our knowledge, this is the first report of a case of keratomycosis caused by *T. roseum*.

CASE REPORT

A 29-year-old white man was struck in his left cornea by a piece of wire, which was extracted by an ophthalmologist in October 1972. A clean wound tract extending through most of the cornea was noted. He was treated with local and systemic antibiotics. Ten days later he was admitted to a community hospital with nonulcerative corneal infiltrate, hypopyon, and uveitis. Treatment with topical corticosteroids, polymycin, atropine, and sulfacetamide eyedrops, and orally administered penicillin, was started. Ten days later the patient developed a corneal ulcer, smears of which revealed mycelia. He was treated with topically applied 30% amphotericin eyedrops, sulfacetamide eyedrops, and atropine; corticosteroids were discontinued.

A descemetocele developed and he was referred to us Dec. 12, 1972. Ocular examination revealed a large central infiltrate in the left cornea (Fig. 1) with purulent debris on the corneal surface and a hypopyon. Systemic examination was normal. Visual acuity was L.E.: hand movements at 1 meter, and R.E.:20/20. Corneal scrapings revealed spores and hyphae. Despite treatment with nystatin eyedrops, antibiotics, and pimaricin, the corneal stromal infiltrate failed to respond to therapy. As perforation appeared imminent, an 8.0-mm penetrating corneal transplant was performed to encompass the entire area of infiltration. The postoperative recovery was uncomplicated and, on his last examination on April 3, 1975, visual acuity was 20/35. He had no recurrence of corneal infection or stromal infiltrate in the three years since surgery.

From the Department of Pathology and the Cornea Service, Wills Eye Hospital (Drs. Rodrigues and Laibson), and the Center for Disease Control, Health Administration, Department of Health, Education and Welfare, Atlanta, Georgia (Dr. Kaplan). This study was supported by a grant from the Elizabeth King Trust and the Pennsylvania Lions Eye Research Foundation, Philadelphia.

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RESULTS

Mycology examination—The corneal scrapings on Sabouraud's agar demonstrated a relatively slow-growing fungus. The colony was flat, velvety, and white and the reverse was rose. Microscopically, there were hyaline hyphae and the conidiophores were long, septate, simple, and erect. The conidiogenous cells were arranged in whorls directly on the conidiophores, and consisted of an elongated, slightly swollen basal part and a tapering rachis-like, conidia-bearing portion. Oval, hyaline conidia, 2.5 to 3.5 × 5.0 to 5.5 μ, were formed alternately along

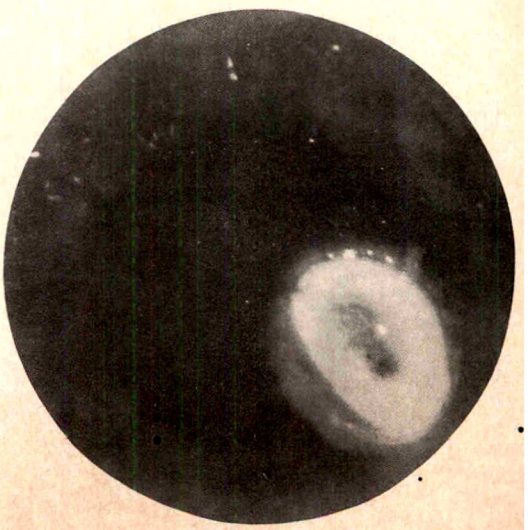


Fig. 1 (Rodrigues, Laibson, and Kaplan). Left cornea showing a paracentral corneal ulcer with marked opacification.

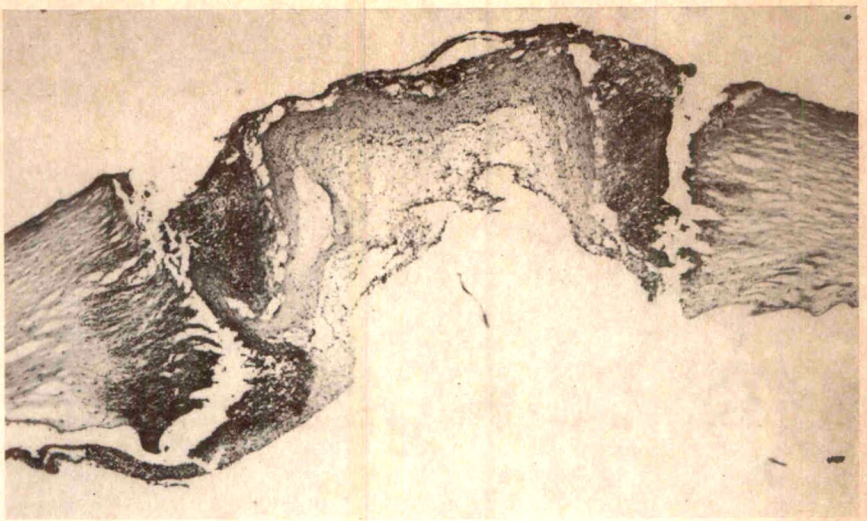


Fig. 2 (Rodrigues, Laibson, and Kaplan). Necrotic corneal ulcer with descemetocele (hematoxylin and eosin, ×25).

the sides of this rachis-like part. The fungus was identified as *T. roseum* by cultural and microscopic characteristics.

Histopathology—The 8-mm corneal button showed a paracentral area of perforation. Formalin-fixed paraffin sections were stained with hematoxylin and eosin, PAS, Brown-Brenn, and methenamine-silver nitrate. Microscopic examination revealed marked necrosis and acute inflammation of all the corneal layers in the area of ulceration (Fig. 2). Centrally, the epithelium was thinned and edematous. Bowman's membrane was partly disrupted. The stroma was infiltrated with polymorphonuclear leukocytes, and was markedly necrotic centrally. Descemet's membrane was disrupted at the site of perforation (Fig. 3). The endothelium was absent.

Examination of PAS- and methenamine-silver nitrate-stained sections showed invasion of the cornea by branched and septate hyphae, ranging from 3.5 to 6.5 μ wide. Many of the filaments were composed of a chain of spherical dilated cells (Fig. 4). Examination of the hematoxylin and eosin-stained sections showed that the fungal elements were hyaline. The margins of the specimen showed no evidence of fungi. Special stains for bacteria were negative. Fluorescent antibody tissue stains for *Candida* and for *Sporothrix* species were negative.

Discussion

Tritirachium roseum has been infrequently

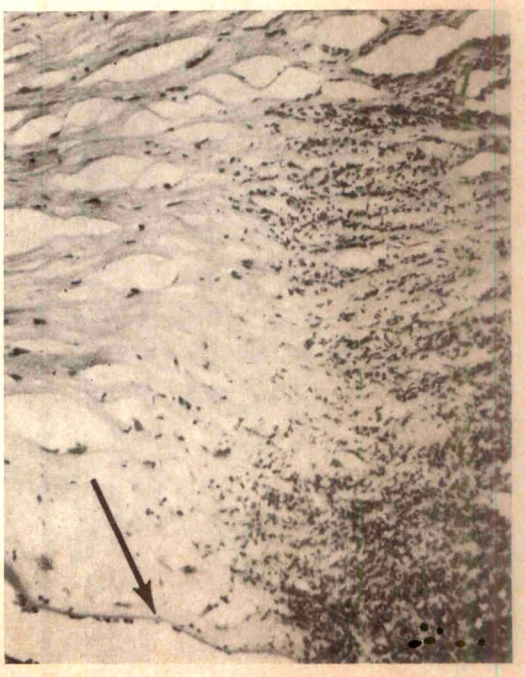


Fig. 3 (Rodrigues, Laibson, and Kaplan). Margin of corneal ulcer showing acute inflammatory infiltrate. Descemet's membrane (arrow) is thinned (hematoxylin and eosin, ×100).



Fig. 4 (Rodrigues, Laibson, and Kaplan). Septate mycelia in the necrotic corneal stroma (Gomori's methenamine-silver nitrate, ×400).

reported from environmental substrates. This ubiquitous saprophytic fungus was first isolated from litter in a cow barn in Kiel, Germany.[3] It has also been recovered from soil in Ontario, Canada, and from the former Belgian Congo.[4] Although *Tritirachium* species appear to be saprophytic in nature, they may occasionally be pathogenic. A fungus identified as *T. brumpti* was isolated from a 17-year-old European girl with keratoconjunctivitis who resided in Cairo, Egypt.[5]

In our case, the fungus was probably introduced into the eye at the time of the initial trauma. This form of exogenous keratomycosis has been frequently observed.[6,7]

Topically applied corticosteroids have stimulated proliferation of opportunistic fungi, especially in the presence of bare stroma.[8] In the present case, treatment with topical corticosteroids before the diagnosis of mycotic infection may have depressed normal protective mechanisms, resulting in the rapid deterioration of the corneal condition.

There has been considerable progress in the therapy of mycotic infections.[9] In our patient, keratomycosis was too advanced for a successful response to pimaricin. However, a penetrating keratoplasty resulted in normal vision without recurrence of infection.

Summary

A 29-year-old white man developed a corneal ulcer following trauma to his left cornea by a piece of wire. *Tritirachium roseum*, a saprophytic fungus, was cultured from corneal scrapings and demonstrated in the corneal button by histopathologic examination.

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ADULT CYTOMEGALOVIRUS INCLUSION RETINO-UVEITIS

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Cytomegalovirus (CMV) inclusion disease, once thought to be principally an intrauterine or neonatal affliction, has been increasingly recognized to occur in adults. This may be largely a result of the more common use of various modalities of immunosuppressive therapy.

In our patient, a case of bilateral ocular involvement by CMV was initially suspected on the basis of characteristic clinical findings, increasing serum complement-fixation antibody titers to CMV, and recovery of virus from the urine and throat. The clinical diagnosis was further supported by the recovery of virus from the aqueous humor. The eyes later became available for histopathologic study, and the presence of viral particles was demonstrated by electron microscopy.

CASE REPORT

A 25-year-old man was first seen here in December 1970 for evaluation of renal insufficiency. In 1953, at age 8 years, he had suffered a gunshot wound to the abdomen in the pancreatic region, and a pancreatic fistula developed with a draining sinus, which eventually closed. Some time between 1960 and 1965, he had an unexplained episode of hematemesis. In April 1968, surgical exploration for an acute abdominal condition revealed an intramural hemorrhage of the bowel; this was believed to have resulted from an accumulative exposure to anticoagulants that he had been using for rodent control. Hematuria was first noted at that time. In July 1968, he experienced massive bleeding from the upper gastrointestinal tract; abdominal exploration revealed portal hypertension and fibrosis in the region of the pancreas. The postoperative course was complicated by jaundice believed to be hemolytic. Between 1970 and 1972, a progressive decrease in renal function produced a nephrotic syndrome; bilateral nephrectomy was performed in December 1972. Histopathologic study showed end-stage chronic proliferative and sclerosing glomerulonephritis with interstitial nephritis.

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On Feb. 7, 1973, he received a renal transplant from his sister and was placed on immunosuppressive therapy (azathioprine [Imuran], 100 mg/day, and methylprednisolone sodium succinate [Solu-Medrol], 40 mg and 80 mg intravenously on alternate days). Virologic studies were begun prospectively and were continued. On March 15, a vesicular lesion was noted on his lip and other lesions subsequently developed on the soft palate; cultures from these yielded herpes simplex virus. Lesions healed completely within a month. In May, his postoperative course was further complicated by *Pneumocystis carinii* infection of the lungs, *Bacteroides fragilis* septicemia, acute hepatitis, and continued weight loss.

Ophthalmoscopic consultation was requested on June 13, to look for possible ocular evidence of subacute bacterial endocarditis. Visual acuity was normal but three soft, white exudates were seen in the right fundus (superotemporally and inferotemporally) and one was seen superotemporally in the left fundus near the optic disk. On July 5, the lesions in the right eye appeared to be more confluent but otherwise essentially unchanged. Two weeks later, there was a gradual decrease in vision of the left eye. On July 25, visual acuity was normal in the right eye but had decreased to finger counting in the left eye. A broad exudative lesion was seen in the posterior pole of one eye inferior to the macula; in the left eye there was extensive edema and retinal infarction involving much of the temporal retina.

One of us (D.M.R.) saw the patient on Aug. 8. Visual acuity was R.E.: 20/25, and L.E.: no light perception. Applanation tensions were 11 mm Hg in both eyes. The anterior chamber of the right eye contained a moderate number of cells and flare with many small keratic precipitates. The anterior chamber of the left eye had marked flare and cells with hypopyon (Fig. 1). Ophthalmoscopic examination of the right eye showed a large white intraretinal exudate below the macula with some intravitreal extension and associated perivenous sheathing (Fig. 2, top). Similar areas of intraretinal exudate were noted in the peripheral retina superotemporally (Fig. 2, bottom). Clumps of cells also were seen on the posterior face of the detached vitreous body. The optic nerve was normal. The left eye showed a massive exudative retinal detachment with much intraretinal and intravitreal exudate and many small intraretinal hemorrhages. A CMV infection was suspected and, on Aug. 9, we performed an anterior chamber paracentesis of the left eye in an attempt to recover organisms. Cultures of the aqueous humor were negative for bacteria, fungi, and yeast, but virologic cultures yielded CMV.

Fever, weight loss, and general deterioration

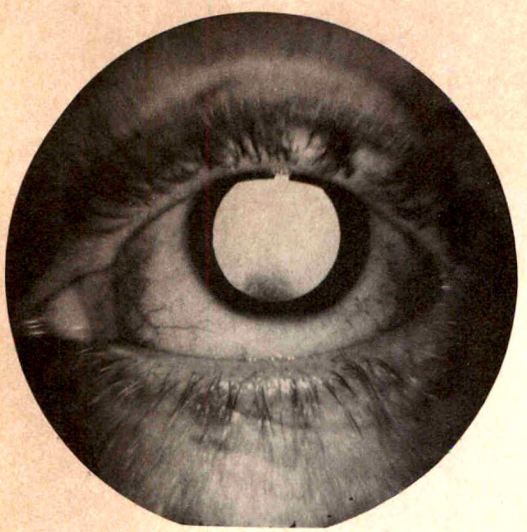


Fig. 1 (Chumbley and associates). Left eye on Aug. 8, 1973, showing layered hypopyon and area of keratic precipitates visible from 5 to 7 o'clock against red reflex.

continued. Blood cultures were positive for *Serratia marcescens* and *Pseudomonas aeruginosa*. An eye examination on Sept. 9 revealed a dilated right pupil with minimal response to direct light and a smaller pupil on the left bound down by posterior synechiae. The right macula showed necrotic retinal exudation. Coma subsequently ensued and the patient died two days later.

The autopsy report gave the following anatomic diagnoses: (1) gram-negative septicemia clinically, multiple small abscesses in lungs, spleen, liver (culture: *Ps. aeruginosa*); (2) bilateral bronchopneumonia and pulmonary edema (cultures: *Ps. aeruginosa*, CMV, and *Aspergillus fumigatus*); (3) subacute and chronic recurrent pancreatitis with massive fat necrosis and calcification of pancreatic and peripancreatic tissue; (4) acute tubular necrosis, no rejection, and intact arterial and venous anastomoses in renal allograft; (5) acute cerebral abscesses (aspergillosis); (6) focal bile plugs, focal necrosis of liver parenchymal cells, sepsis, and extrahepatic obstruction; and (7) old thrombosis of terminal superior mesenteric vein.

Methods

Viral culture—Specimens for culture (urine, throat, aqueous humor, autopsy tissue suspension) were inoculated into WI-38 (0.25 ml), HeLa (0.3 ml), and primary rhesus monkey kidney (0.3 ml) cell cultures.[1] The presence of CMV was recognized by characteristic cytopathic effects only in WI-38 cell cultures. Typical inclusion-bearing WI-38 cells were seen after staining with hematoxylin and eosin.[1] In the absence of cytopathic effects in the WI-38 cell cultures within the first 14 days, the cells were transferred to fresh cultures and observed weekly for four to six weeks for the presence of CMV infection.

Serology—Commercially available complement-fixation antigen (AD-169 strain) was used in the microtiter technique[2] to measure antibody to CMV.

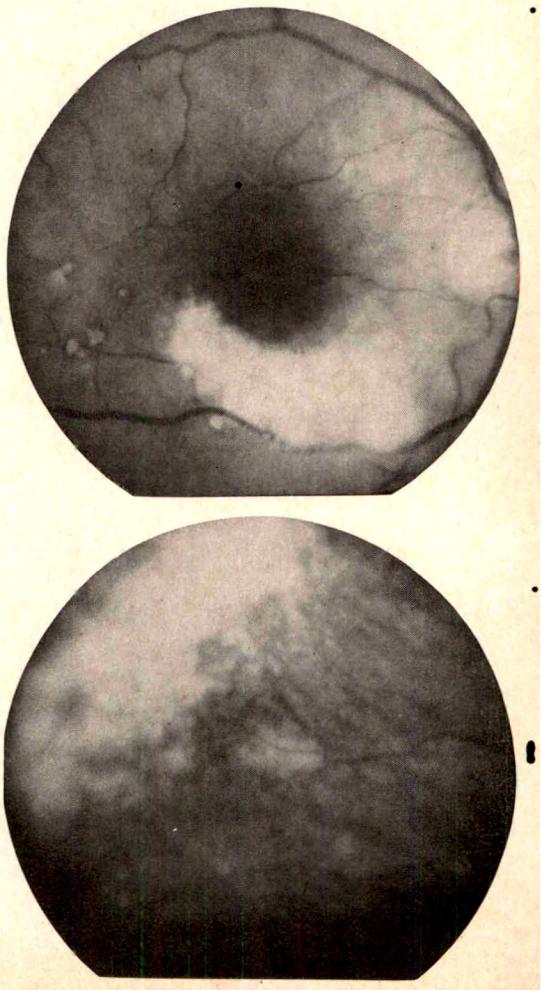


Fig. 2 (Chumbley and associates). Fundus photographs of right eye on Aug. 8, 1973. Top, Discrete white lesion of necrotic retinitis is present inferior to macula; small lesions to the left are precipitates on detached posterior vitreous body. Bottom, Superior temporal portion has white, necrotic lesion with white dots. Area of perivascular involvement is seen just in advance of lesion.

Pathology—The eyes obtained at autopsy were fixed in formaldehyde-glutaraldehyde solution and then opened in the horizontal plane. Sections were cut, 8 μ thick, and stained with hematoxylin and eosin, silver chromate, Brown and Best Gram stains, and PAS reaction. A portion of the nasal calotte of the right eye was prepared by standard techniques for electron microscopy.

Results

Virus studies—The patient was seronegative for complement-fixing CMV antibody at the time of renal allograft transplantation and on four later tests during the first month (Fig. 3). However, 2½ months after transplantation, antibody to CMV developed. Subsequently, the titer increased. Ten days after the detection of CMV antibody, CMV was isolated from the urine. The virus was isolated from urine on five other occasions (Table).

Cytomegalovirus was isolated (Fig. 4) from aqueous humor of the left eye and also from autopsy specimens from the lung, esophagus, and kidney.

TABLE

Results of virologic studies

Date	Source
	Cytomegalovirus
4/27/73	Urine
6/13/73	Urine
6/15/73	Urine
6/20/73	Throat
6/28/73	Urine
7/30/73	Urine
8/9/73	Aqueous humor, LE
8/27/73	Urine
	Herpes simplex virus
3/3/73	Oral gum ulcer
3/5/73	Throat
3/16/73	Lip
5/25/73	Sputum
6/13/73	Nose
7/5/73	Mouth and tongue

Gross pathology—There was no abnormality of the anterior segment of the right eye. Suspended within the vitreous body were grayish white flecks that were more numerous anteriorly and inferiorly. A grayish white, fine membrane covered the optic

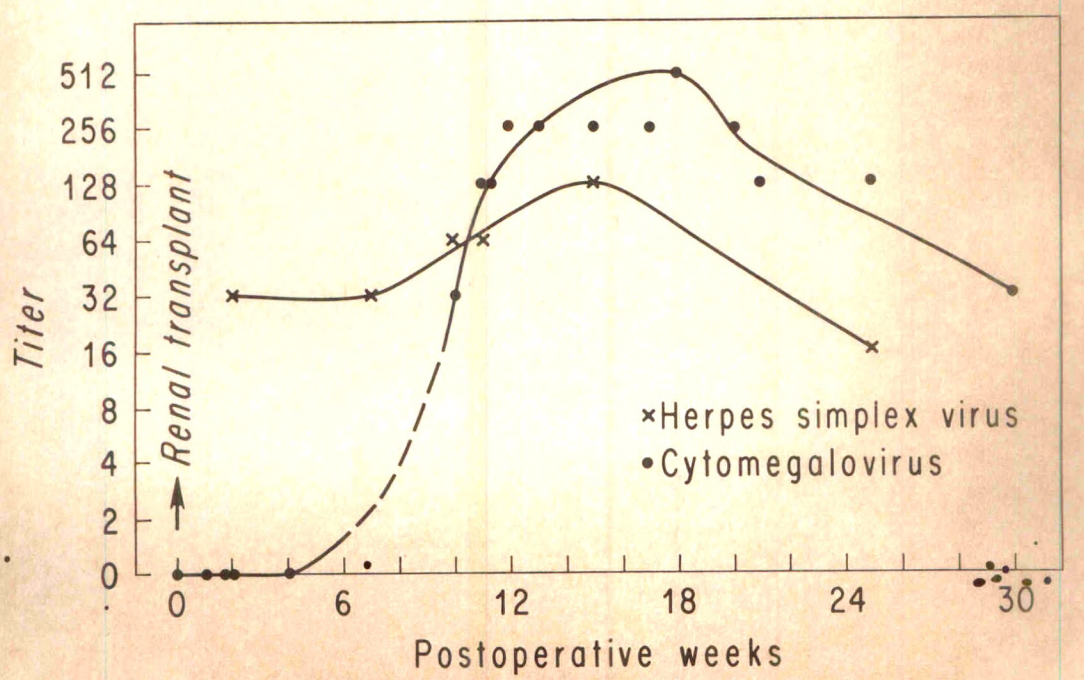


Fig. 3 (Chumbley and associates). Titers of antibodies to CMV and herpes simplex. Time zero is date on which renal transplantation was performed.

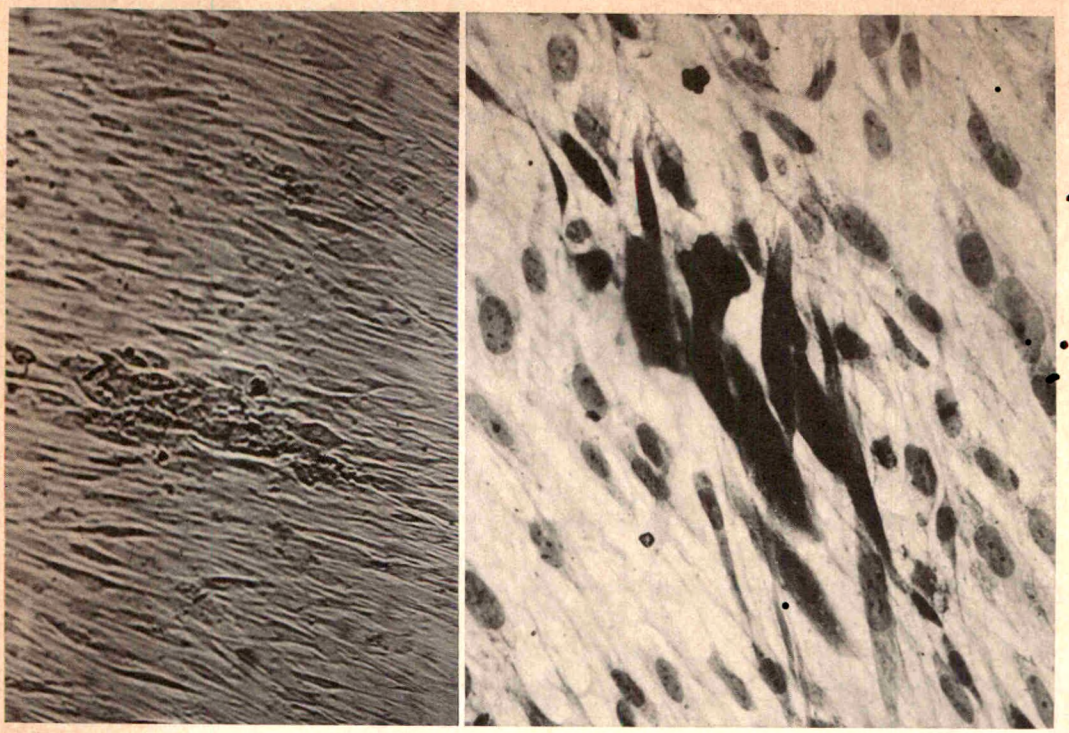


Fig. 4 (Chumbley and associates). Left, Cytopathic effects produced in WI-38 by CMV from eye specimen (×125). Right, CMV inclusion in cells from WI-38 cultures (hematoxylin and eosin, ×400).

disk. The retina was partially detached from the temporal side by yellowish white, subretinal exudate.

Posterior synechiae were present in the left eye. The vitreous cavity was almost completely filled by soft, friable, yellowish gray tissue that partially replaced the retina; the true retinal layer was identified only anteriorly for a short distance immediately posterior to the pars plana. The disk could not be seen. The vitreous body was partially detached, and numerous grayish white flecks were scattered randomly throughout.

Light microscopy—A few keratic precipitates were present in the right eye. Within all retinal layers were focal collections of large cells with intranuclear and intracytoplasmic inclusions (Fig. 5, top). The adjacent choroid was infiltrated by lymphocytes, plasma cells, and monocytes. Many zones of retinitis were sharply demarcated from normal retina (Fig. 5, bottom left). Neither the exudate covering the disk nor the precipitates of inflammatory cells within the vitreous body contained inclusion bodies (Fig. 5, bottom right).

The posterior retina of the left eye was completely necrotic. No inclusion-bearing cells could be seen within this necrotic layer. There was a diffuse choroidal infiltration of mononuclear cells with a few inclusion-bearing cells and an occasional focus of necrosis (Fig. 6, left). Numerous cellular precipitates consisting of lymphocytes and plasma cells were scattered throughout the vitreous body; no inclusions were identified within these. The vessels within the optic nerve showed a perivascular mononuclear inflammatory infiltrate (Fig. 6, right).

Cytomegalovirus inclusions were also seen in the lung, kidney, and pancreas.

Electron microscopy—The intranuclear inclusions in the right retina consisted of granular electron-opaque aggregates of chromatin arranged in a lacelike pattern. These were surrounded by an electron-

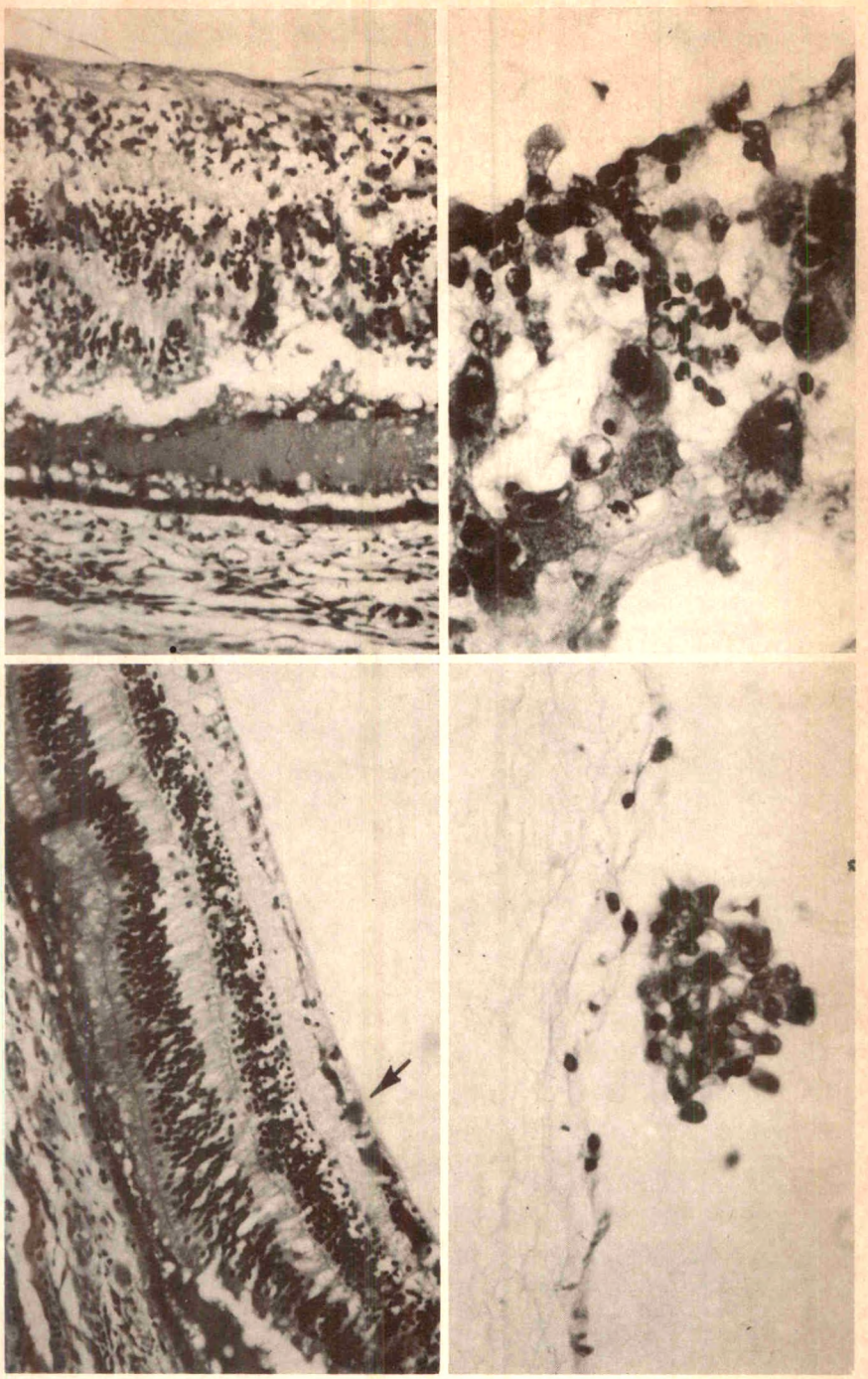


Fig. 5 (Chumbley and associates). Sections from right eye. Top left, Abundant CMV inclusions in retina, varying degrees of retinal disorganization, subjacent detachment of sensory retina, and relative integrity of retinal pigment epithelial layer and choroid (hematoxylin and eosin, ×10). Top right, Typical Cowdrey type-A intranuclear inclusions with surrounding halo within retina; diffuse granular cytoplasmic inclusions also are present (hematoxylin and eosin, ×40). Bottom left, Leading edge of retinal lesion, with CMV inclusions, beginning destruction of retinal architecture, and expanding subretinal exudate sharply demarcated (arrow) from normal retina in advance of lesion (hematoxylin and eosin, ×10). Bottom right, Clumped inflammatory cells on detached posterior vitreous body (hematoxylin and eosin, ×25).

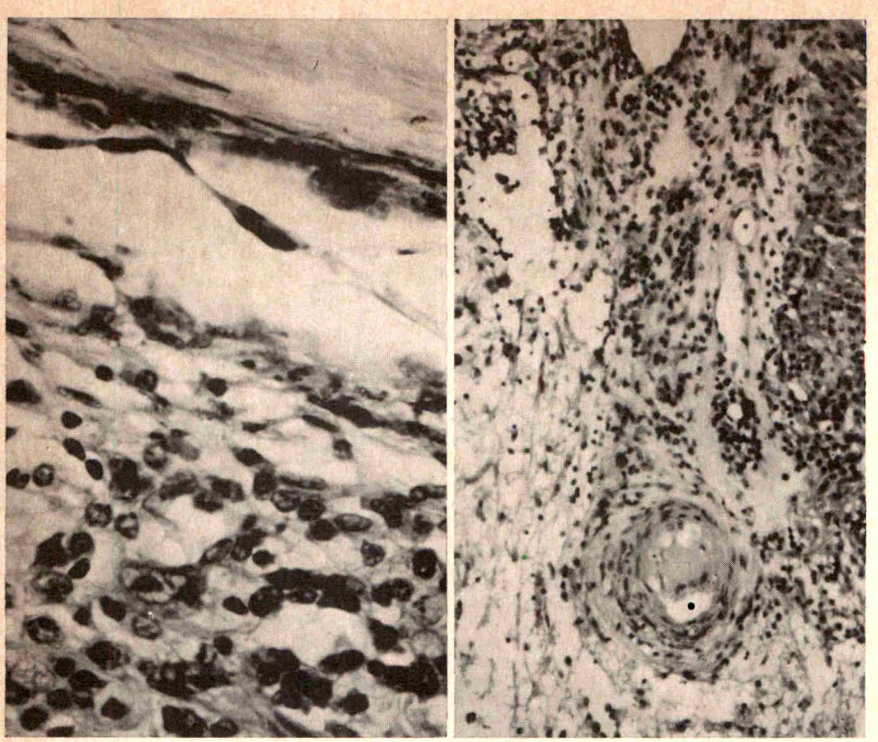


Fig. 6 (Chumbley and associates). Sections from left eye. Left, Choroid has round cell infiltration with single CMV inclusion-bearing cell. Sclera is at top (hematoxylin and eosin, ×40). Right, Left optic nerve shows perivascular cuffing by inflammatory cells (hematoxylin and eosin, ×10).

lucent halo. Numerous viral particles were freely interspersed in the interstices of the chromatin aggregates within the nuclear inclusions. Some were also scattered loosely in the halo zone (Fig. 7). The viral particles were spherical, sometimes having both an outer and an inner electron-opaque membrane with either an electron-lucent or electron-opaque core.

The cytoplasmic viruses were seen both as isolated forms and as clumps within inclusions. The viral clumps without an electron-opaque core had either a nucleocapsid alone or a nucleocapsid and an additional electron-dense envelope. The latter forms were frequently associated with large, dense, cytoplasmic particles (Fig. 8).

Discussion

Seventy years have elapsed since the initial description of the cytomegalic inclusions in an infant[3] (thought then to be caused by protozoa) and more than 50 years have passed since Goodpasture and Talbot[4] asserted that the changes seen must be due to a viral agent (about the same time as the first description of ocular involvement by CMV in an infant).[5]

In the late 1950s, CMV was finally proved to be the etiologic agent in cytomegalic inclusion disease in man by three independent groups of workers,[6-8] and at about this same time the first case of ocular cytomegalic inclusion disease in an adult was reported by Foerster.[9] Since that time there have been at least eight reports of proved cases of ocular cytomegalic inclusion disease.[10-16] Additionally, there have been several cases in which CMV was the presumptive cause of the ocular involvement.[13,17] De Venecia and associates[12] were the first to demonstrate the histopathologic findings with elec-

tron microscopy and clearly correlate these findings with the clinical picture. Burns,[18] the first to culture CMV from an eye, recovered it from the aqueous humor of a neonate who had moderate to marked posterior uveitis and mild anterior uveitis. Cytomegalovirus has also been recovered from subretinal fluid from an adult renal

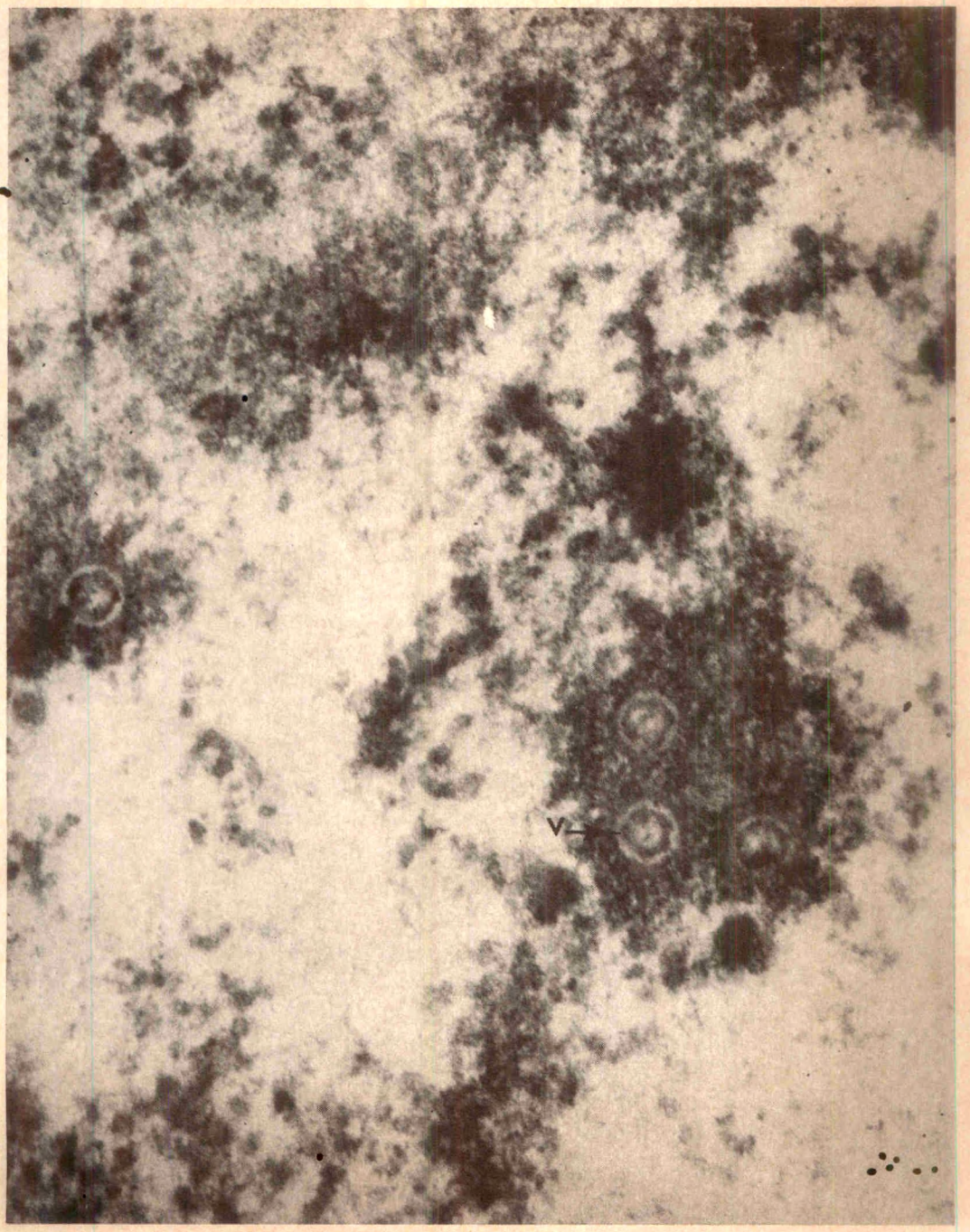


Fig. 7 (Chumbley and associates). Electron micrograph of right retina shows part of intranuclear inclusion with scattered granular matrix of aggregated chromatin containing viral particles (v) (×25,661).

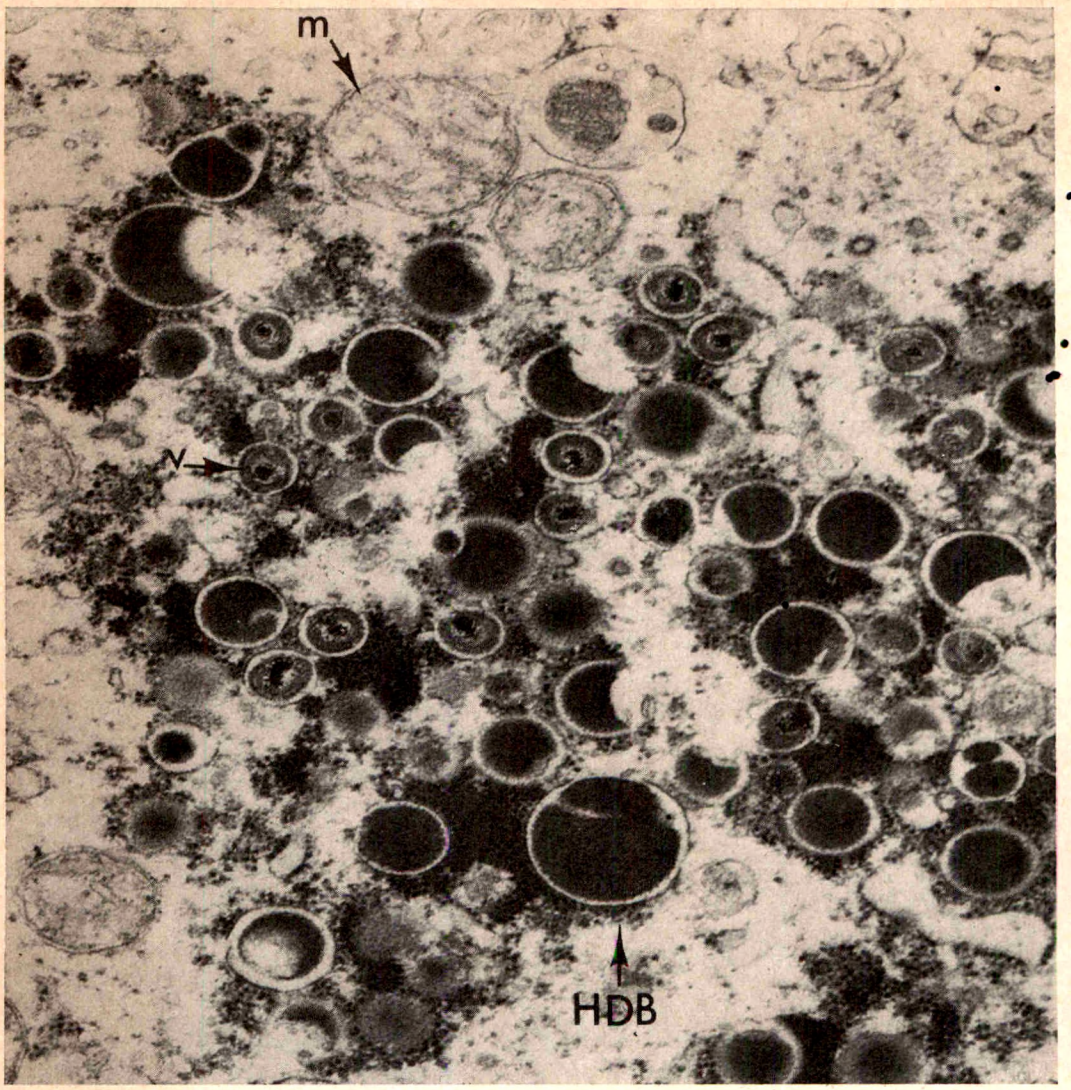


Fig. 8 (Chumbley and associates). Cytoplasmic inclusion from right retina demonstrates viral structural components, homogeneous dense bodies (HDB), and numerous completely assembled mature virions (v). Numerous mitochondria (m) are present (×5,731).

transplant recipient who had a rhegmatogenous and exudative retinal detachment.[13] Our patient is the first adult in whom CMV has been cultured from aqueous humor, and is the first case in which a combination of clinical observation, serologic documentation, cultural proof, and pathologic (including electron microscopic) examination has been achieved.

The ophthalmoscopic appearance of the retinitis in this case was consistent with other reported descriptions.[10,12,13] The initial lesions were scattered white patches that later became confluent; granular white patches were visible adjacent to the confluent lesions and were associated with sheathing of adjacent retinal vessels. The retinal lesions assumed the shape of broad linear infarctions with a sharply demarcated advancing edge. This abrupt transition between the normal and the advancing necrotic retina was clearly demonstrated histopatho-

logically. We did not see a trailing zone of healing retina, presumably because the rapid progression of the disease did not allow time for this to develop. In addition to the retinitis, both eyes eventually developed exudative retinal detachments.

Histologic examination revealed the presence of numerous inclusion-bearing cells scattered throughout the retinas of both eyes. Such cells were absent from subjacent choroid except in areas with massive retinal destruction. In general, these findings support the suggestion of Wyhinny and co-authors[14] that Bruch's membrane is a resistive barrier to viral spread.

Mutton-fat-like precipitates on the detached posterior vitreous face were also seen and examined histologically but these precipitates did not contain cytomegalic inclusion-bearing cells.

The ultrastructural findings in this case were similar to previous clinical and laboratory observations.[12,14,19-22] Viral elements were present in a variety of forms and stages of maturity within both the nucleus and the cytoplasm of the diseased retinal cells. In both nucleus and cytoplasm, mature forms consisted of a core (composed of DNA) that varied in development from a ring to a dense sphere surrounded by a nucleocapsid. After penetration into the cytoplasm, the virus often gained a further thin outer electron-dense coat or envelope.[19-22]

What are the circumstances that might lead to infection by CMV? Because CMV is ubiquitous, exposure to the virus is commonplace. Subclinical infection apparently is responsible for the high incidence (92%) of CMV antibody in persons over 50 years of age in the general population, in contrast to its rare presence in preschool children.[23] Our patient had no demonstrable complement-fixing CMV antibody titer initially, and so the progressive increase in antibody titer probably was a consequence of primary infection; however, reactivation of latent CMV infection cannot be completely excluded.[24]

Each of the three presumed cases[13,17] and five of nine proved cases[10,12-14,16] of ocular cytomegalic inclusion disease in adults, including our case, have occurred in renal transplant recipients. In a retrospective survey of autopsy material from renal transplant recipients, Kanich and Craighead[25] showed conclusively that the disease was associated with immunosuppressive drug treatment. Systemic corticosteroid administration has also been shown to accelerate experimental CMV infection in mice.[26] Because the number of renal transplant patients is increasing annually[27] and because immunosuppressives and systemic corticosteroids are generally used, we expect to see more instances of postoperative ocular involvement by CMV in renal transplant recipients or in any debilitated patient receiving immunosuppressive therapy with or without systemic corticosteroids. The clinician must be alert to such a possibility in the appropriate clinical setting.

Summary

A 27-year-old male renal transplant recipient acquired cytomegalovirus (CMV) infection of both eyes. This was characterized early by a distinctive necrotic retinitis with discrete advancing edges. A large exudative retinal detachment and hypopyon developed in one eye, and cultures from the anterior chamber aspirate grew CMV. Cytomegalovirus was also isolated from the urine and throat; after serial negative base-line titers, CMV antibody titer became positive. At autopsy CMV was isolated from lung, esophagus, and kidney tissue. Light and electron microscopic studies demonstrated extensive necrosis and disruption of the sensory retina and retinal pigment epithelium with exudative retinal detachments. The diseased retinal cells contained a multiplicity of viral particles in various stages of maturity. Cytomegalic inclusion-bearing

cells were demonstrated in the choroid of the more severely affected eye.

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CYTOMEGALOVIRUS IN TEARS FROM PATIENTS WITH NORMAL EYES AND WITH ACUTE CYTOMEGALOVIRUS CHORIORETINITIS

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Infection with cytomegalovirus (CMV) may cause subclinical infection or overt illness known as cytomegalic inclusion disease (CID). Most infections are asymptomatic but serious disease may occur in the unborn infant and the immunosuppressed host. Congenital CID is characterized by a syndrome of prematurity, microcephaly, intracranial calcifications, chorioretinitis, optic atrophy, hepatosplenomegaly, anemia, and thrombocytopenia.[1] Postnatally acquired infection occurs most commonly in patients with generalized malignancies or leukemia[2] and in renal transplant recipients.[3,4] Infection typically results in a fever with an exanthematous rash, pneumonitis, or hepatitis.[5]

Involvement of the eye in CID has been frequently described in congenitally infected patients,[6-17] the main feature of the disease being a chorioretinitis with secondary optic atrophy. Chorioretinitis with acquired CMV infection occurs rarely and only eight cases have been described.[4,18-23] These have occured in one adult whose general health was not described,[18] in three adults with Hodgkin's disease,[19,20,23] and in four renal allograft recipients.[4,21,22] No cases have been described in children. Few attempts have been made to correlate the cultural isolation of CMV with the clinical or pathologic features of CMV chorioretinitis.[8,22] The presence of CMV in tears has not been documented[24] and previous attempts at isolation have been unsuccessful.[22] We describe the isolation of CMV from tears, its relationship to chorioretinitis in a group of children with congenital and acquired CMV infections, and attempts at therapy.

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Materials and methods

Forty-one children who were excreting CMV in their urine or saliva were examined from Dec. 27, 1972, to March 19, 1974, for the presence of chorioretinitis and we obtained cultures of the tears or conjunctival sac for CMV at the same time. Of the 41 children, 33 had acute lymphocytic leukemia, five had acute myelocytic leukemia, one had systemic lupus erythematosus, one had sickle cell anemia, and one infant had congenital CID. The group included 19 males and 22 females ranging in age from 6 months to 19 years. There were five black and 36 white children.

Tear cultures were obtained at the time of clinic visits until all patients were tested. Repeated tear cultures were taken at monthly intervals in patients with chorioretinitis and sporadically in other patients. Peripheral blood leukocyte cultures were done on 35 patients as part of another study.

Tears were collected on a sterile cotton-tipped applicator until it was saturated (approximately 0.15 ml) and were usually obtained when patients were crying during painful procedures, such as bone marrow aspiration. In lieu of lacrimation, the conjunctiva was washed with several drops of sterile normal saline (without preservatives) and removed with the cotton-tipped applicator at the inner or outer canthus. Saliva samples were obtained similarly by swabbing

the buccal and sublingual areas of the mouth. The swabs were placed into a sterile plastic centrifuge tube containing 2.0 ml of transport media (Hank's balanced salt solution containing 2% fetal bovine serum). Swabs were compressed against the tube before removal in order to retain the maximum amount of inoculum. Urine samples were freshly voided and routinely collected. Specimens were kept at 4°C and inoculated within four hours of receipt in the laboratory. Most specimens were processed immediately.

Urine samples were processed by the addition of 10,000 units of aqueous penicillin G potassium, 2,000 μg of streptomycin sulfate, and 20 μg of amphotericin B to each milliliter. The tear and saliva samples were placed in a refrigerated centrifuge at 4°C and spun at 150 g for 20 minutes. The supernatant fluid was decanted, and the same antibiotics were added. All specimens were kept at 4°C for one hour and inoculated in 0.3-ml amounts into each of three 16 × 150-mm test tubes containing human embryonic lung fibroblasts growing in tissue culture. Aqueous humor was inoculated directly without preparation. Eagle's medium containing aqueous penicillin G potassium (50 units/ml), streptomycin sulfate (50 μg/ml), nystatin (Mycostatin) (25 units/ml), and 2% fetal bovine serum was used for maintenance. The medium was changed after absorption for one hour at 37°C and twice weekly thereafter.

Leukocyte cultures were performed on 10 ml of heparinized blood collected in a plastic syringe and allowed to sediment in an upright position at 37°C for two hours. The leukocyte-rich plasma was removed, and the leukocytes were separated by centrifugation. After removal of the plasma, the leukocytes were washed three times with 5.0 ml of maintenance media. A final suspension was made in 3.0 ml of media and 0.1 ml was used as the inoculum in each of four tubes.

Tissue samples were obtained at autopsy, and 0.1- to 0.2-g pieces were washed three times with maintenance medium, and a 10 to 20% suspension was then made by grinding in a glass homogenizer. The homogenate was centrifuged, and 0.3-ml aliquots of the supernatant were inoculated in each of three tubes.

Cultures were examined two or three times a week for cytopathic effect and maintained for four weeks before being read as negative. The typical, focal cytopathic effect of large, rounded cells was used to identify CMV. All isolates were passed once into Leighton tubes with human embryonic lung fibroblasts. After the cytopathic effect developed, coverslips were stained with hematoxylin and eosin and examined for the characteristic intranuclear and intracytoplasmic inclusions.

Complement fixation (CF) tests were performed by the standard microtechnique[25] employing the AD-169 strain of CMV as the antigen.

Patients receiving chemotherapy for CID were monitored by daily physical examination and the performance of the following liver function tests: serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), and alkaline phosphatase (AP); the following renal function tests: blood urea nitrogen, serum creatinine, and urinalysis; and a white blood cell count (WBC), hemoglobin determination, platelet count, and reticulocyte count. After treatment they were tested and examined one to three times per week for two to three weeks.

Results

A total of 130 tear cultures were done on the 41 children during the 15-month study period, and virus was present on 17 occasions in eight patients (19.5%) who had acute lymphocytic leukemia. Seven of the eight children had viremia before or after the isolation of virus in tears. Seven of 29 (24%) other patients had viremia.

Repeated cultures (two to four) were needed to detect the presence of virus in tears in some cases since excretion was

intermittent. The conjunctival wash was as effective as collecting tears in determining the presence of virus when both methods were used in the same patient. Five of the eight tear excretors were asymptomatic and developed no retinal disease during nine to 15 months of observation. Two died during the study, and examination of the lacrimal gland in one revealed extensive interstitial infiltrates of leukemic cells and variable numbers of plasma cells but no inclusion-bearing cells.

Chorioretinitis was observed in five patients with active lesions, evidenced by recent exudates and hemorrhages, in three patients who had virus in tears. Two patients with small focal areas of old chorioretinitis had no virus in tears and never developed progression of their disease in 15 months of observation. All five patients had negative fluorescent antibody titers to *Toxoplasma gondii,* and four had negative CF antibody titers to *Histoplasma capsulatum.* The fifth patient, who had inactive disease, did not undergo a CF test for *H. capsulatum.* A CF titer for CMV was 1:8 two months after diagnosis in one patient with healed chorioretinitis, and 1:256 in another patient four months before diagnosis. One patient with active lesions had a CF titer to CMV of 1:2,048 two months after diagnosis, and two patients had a titer $\geqslant$ 1:8 at the time of diagnosis.

Clinically active ocular disease developed after 13 to 27 months of chemotherapy during hematologic remission of leukemia and progressed to blindness (20/200 visual acuity) or severely diminished vision in the diseased eye in the three patients. Elevated serum levels of IgM were present in all three patients, with hypogammaglobulinemia in two and a normal IgG level in the third. All three patients had viremia with CMV before and after the development of ocular disease. One patient with healed chorioretinitis also had asymptomatic viremia after diagnosis.

Leukopenia ($\leqslant$ 2,000 white blood cells/mm^3) and neutropenia ($\leqslant$ 500 neutrophils/mm^3) were present intermittently during the course of active disease and were related to the onset of retinal lesions in two patients.

Of three patients with active CID, one was treated with idoxuridine (IDU) and two with adenine arabinoside (ara-A). No obvious clinical benefit could be determined in two patients. One patient with atypical disease treated with ara-A (Case 3) possibly had an accelerated recovery.

The patient treated with IDU sustained a modest elevation of the SGOT (175 international units) that began three days after completion of therapy and persisted for two months. The SGPT, AP, and hemoglobin remained normal and the LDH was moderately elevated during this time. Leukopenia (1,000 white blood cells/mm^3) and diminished platelet and reticulocyte count (0.2%) occurred during the ten days after completion of therapy. No abnormalities in renal function were noted and all the side effects disappeared without permanent sequelae.

The two patients treated with ara-A had mild, transient elevation of the SGOT, SGPT, and LDH with no change in the AP or renal function. No change occurred in the WBC or hemoglobin level but the platelet count was mildly diminished in one patient and the reticulocyte count was severely diminished in the other. These changes were noted in the week after treatment and all resolved spontaneously in one to two weeks without ill effects.

Case reports

Case 1—A 5-year-old white boy with acute lymphocytic leukemia developed chorioretinitis of the left eye in July 1972, one year after therapy was instituted. This consisted of superficial macular edema and a focal area of punctate, fine, white spots and traction lines. Visual acuity was R.E.: 20/30 with a normal fundus, and L.E.: 20/80 (dilated). Occasional ocular pain was present. By September, the macula was involved, numerous hemorrhages and white streaked exudates were present, and traction lines were not as marked. Visual acuity was R.E.: 20/30, and L.E.: 20/200. The CF titer to CMV was 1:2,048 at this time. Immunoglobulin determination two months after the onset revealed a low IgG level (440 mg/100 ml) and an elevated



Fig. 1 (Cox, Meyer, and Hughes). Case 1, lacrimal gland. Interstitial infiltrates of plasma cells and lymphocytes are present in a periductal distribution (hematoxylin and eosin, ×480).

IgM level (180 mg/100 ml). Leukopenia and neutropenia were not present.

In November 1972, we administered a five-day course of intravenous IDU. He received a dose of 2.4 g per square meter per day as a 24-hour infusion. Urine, saliva, and leukocyte cultures grew CMV before and after therapy, and no change occurred in the progression of the chorioretinitis. The retinal disease progressed in the left eye until visual acuity was hand motions in January 1973 and light perception by August 1973. Cultures of tears grew CMV on many occasions. In July, chorioretinitis involved the periphery of the retina of the right eye. Healed areas showed no increased pigmentation at the margins.

At autopsy, cultures of both retinas, vitreous humor, lacrimal glands, salivary glands, lungs, and kidneys revealed no CMV. Microscopic sections of the lacrimal glands showed no inclusions but interstitial, periductal infiltrates of lymphocytes and plasma cells were present (Fig. 1). Sections of the retina in both eyes revealed extensive areas of coagulative necrosis with inclusion-bearing cells in all retinal layers (Fig. 2). Typical intranuclear (Cowdry Type A) and intracytoplasmic inclusions were noted with focal collections of inflammatory mononuclear cells, especially plasma cells. Early lesions consisted of a few inclusion-bearing cells in a structurally intact retina. The retinal architecture was severely disrupted in the most acutely involved areas with changes localized to the sensory retina and pigment epithelium (Fig. 2). Adjacent areas showed early focal calcification (Fig. 3). Late atrophic lesions showed a few inclusion cells in dense fibrous tissue replacing the anterior retina with underlying areas of vascular congestion and perivascular accumulations of plasma cells. Bruch's membrane was intact and the choroid was normal. A few inclusion cells were found in the lungs.

Case 2—A 4-year-old white boy had acute lymphocytic leukemia in May 1971. Three months later, a CF titer to CMV was 1:64. Sixteen months later a urine culture revealed CMV. In April 1973, asymptomatic viremia occurred and in June, bilateral chorioretinitis was noted. This was characterized by recent, diffuse, perivascular hemorrhage and exudate in the right eye (Fig. 4) and older, large atrophic areas with some pigmentation involving the macula in the left eye. A culture of tears at this time and on other occasions revealed CMV. Visual acuity was 20/200 in both eyes. Serum immunoglobulin determination revealed a low IgG level of 240 mg/100 ml and an elevated IgM level of 250 mg/100 ml. The CF titer to CMV

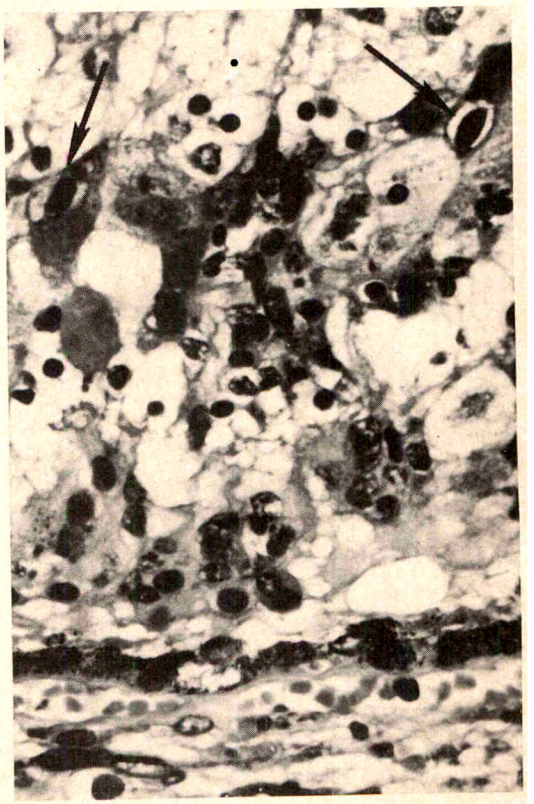


Fig. 2 (Cox, Meyer, and Hughes). Case 1, right retina. Enlarged retinal cells at various levels contain typical intranuclear and intracytoplasmic inclusions (arrows). The retinal architecture is completely disrupted in this area and numerous necrotic cells are scattered throughout the section. Remaining pigment epithelium is at the bottom (hematoxylin and eosin, ×480).

was 1:64 and leukopenia and neutropenia were present. In June, culture of the aqueous humor from the right eye grew no virus.

The patient was treated with ara-A, given as a 12-hour intravenous infusion at a dose of 10 mg/kg per day for 14 days, topical corticosteroids, and gamma globulin. During therapy no obvious change in the chorioretinitis occurred but vision improved slightly and by July, visual acuity was R.E.: 20/100, and L.E.: 20/80-1. The ophthalmoscopic changes remained stable for several months until the patient died. Permission to examine the eyes was not obtained.

Case 3—A 2½-year-old white girl had acute lymphocytic leukemia in May 1971. Ten months later a CF titer to CMV was 1:64. A urine culture revealed CMV in October 1972, and in June and July 1973, asymptomatic viremia was present. In August, a tear culture revealed CMV and the ophthalmoscopic examination was normal. An early area of disciform elevation of the left macula was noted in October when the visual acuity was normal and she was leukopenic and neutropenic. In January 1974, active chorioretinitis, evidenced by recent intraretinal hemorrhage and deep, serous exudate (Fig. 5), was present in the same area of the left eye with an additional lesion at the ora serrata. Visual acuity was 20/200. Repeated tear cultures at this time and subsequently revealed no virus. Serum immunoglobulin determination revealed an elevated IgM level of 250 mg/100 ml and a normal level of IgG. A CF titer to CMV was 1:256. She was not leukopenic or neutropenic.

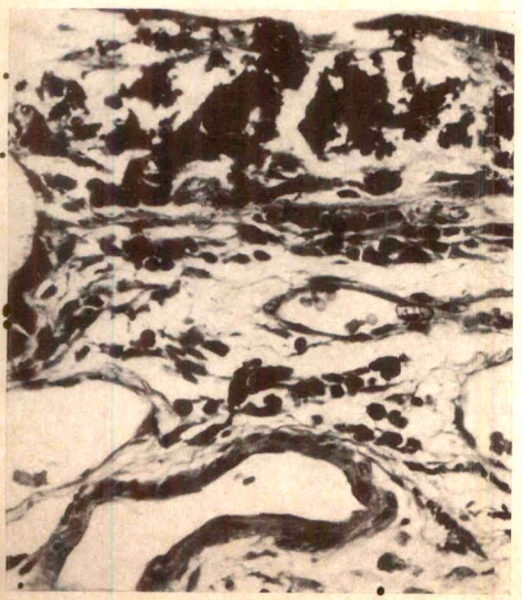


Fig. 3 (Cox, Meyer, and Hughes). Case 1, right retina. Calcification is seen (top) replacing the retina in an area of scar (hematoxylin and eosin, ×350).

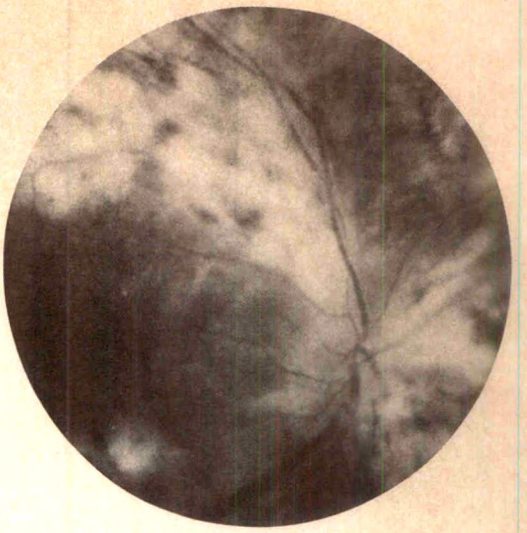


Fig. 4 (Cox, Meyer, and Hughes). Case 2, right eye, June 1973. Acute lesions manifested by multiple areas of perivascular, punctate, confluent, white exudates, and recent focal hemorrhages. Older, atrophic pigmented areas are present superior to the disk.

She was treated with intravenous ara-A given as a 12-hour infusion at a dose of 15 mg/kg/day for ten days. An ophthalmoscopic examination 12 days after completion of therapy revealed a pigmented, healed area of chorioretinitis which has not changed. Visual acuity in the left eye has remained 20/200.

Discussion

Infection of the lacrimal gland in mice by murine CMV has been well demonstrated. Virus has been isolated by grinding infected tissue and from cotton swab cultures of the conjunctival surface during experimental infections.[26] Also, naturally occurring CID has been demonstrated histologically in the lacrimal glands of male laboratory rats.[27] Postnatally acquired CID of man has rarely been described in the lacrimal gland,[28] but in congenital CID, periductal inflammation alone has been noted in the absence of inclusion cells.[29] This study has shown that human CMV is present in tears, although the exact source of virus is not clear. The absence of virus and inclusion cells in the lacrimal glands at autopsy in Case 1 suggests that the source of virus may have been in

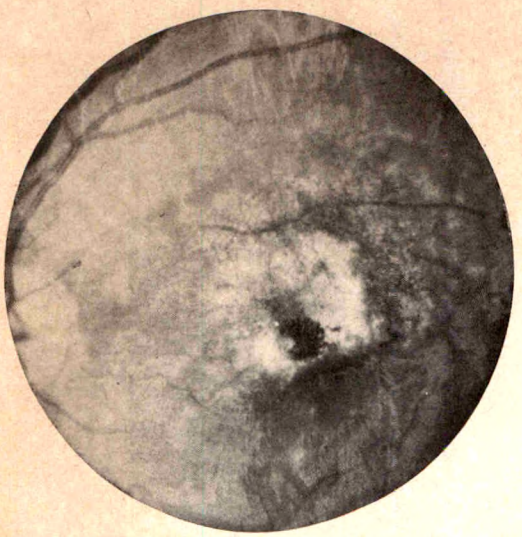


Fig. 5 (Cox, Meyer, and Hughes). Case 3, left eye, Jan. 9, 1974, before ara-A therapy. The previous area of disciform elevation is now involved with punctate, confluent, white exudates and recent focal hemorrhage. The disease was confined to this area alone.

the palpebral lacrimal glands, meibomian glands, or glands of Zeis. Alternately, the periductal, interstitial inflammation may represent the only histologic evidence of infection as previously described.[29] However, the large amounts of virus, as estimated by the number of foci of CPE per tube, excreted by actively crying patients, suggest that the origin is the major lacrimal gland since this produces the greatest volume of tears. The failure to isolate virus from kidney and salivary glands, where virus was present in urine and saliva for many months, may be due to a preterminal event causing cessation of viral excretion, unknown problems in cultural techniques, or substances in postmortem tissue inhibitory to viral growth.

The excretion of CMV was readily demonstrated in tears or in a saline wash of the conjunctival sac. Although no ocular disease developed in five patients with asymptomatic tear excretion during nine to 15 months of observation, a longer study is needed to determine if this is related to the eventual development of CMV chorioretinitis. If this relationship exists, then serial tear cultures in immuno suppressed CMV excretors would be useful in detecting potential ocular disease. Patients with viremia in particular should be examined for tear excretion since six of our 13 (46%) patients with viremia had virus in tears. Further studies of congenitally infected infants and other patients with acquired CMV infection would help determine the spectrum of involvement. The presence of virus in tears also represents another possible method of spread of CMV as suggested by Weller.[24] The clinical appearance in two of the three cases of active chorioretinitis and the pathologic findings in one of them are characteristic of CMV infection.[21,22] The retinal lesion in Case 3 and its progressive activity over a three-month period may represent an earlier type of lesion not previously described. To our knowledge, these are the first three cases of acquired ocular disease reported in children.

The relationship of retinal disease to the presence of CMV in tears is unclear. The three cases of active chorioretinitis were accompanied or preceded by viremia and virus was present in tears while inactive ocular disease in two patients was accompanied by viremia in one and no tear excretion in either. In the inactive cases a definite diagnosis could not be established from the clinical appearance or other laboratory tests. The presence of viremia and the absence of virus in aqueous humor as seen in this study have been previously described in association with active ocular lesions in two renal transplant patients.[22] Previous attempts at tear cultures have been performed on one sample.[22] However, repeated cultures (two to four) should be performed to determine the presence of CMV since the pattern of excretion is intermittent.

Previous studies[21,22] noted the relationship of corticosteroid therapy to the development of chorioretinitis. Only two patients in the present study received prednisone, given as a two-week course every three months. However, none was given three weeks before dis-

ease began in Case 2 or 2½ months before the early lesions appeared in Case 3. It appears that CMV chorioretinitis develops readily in the absence of corticosteroid therapy.

The elevated IgM levels in our two patients suggest recent infection but CMV-specific IgM determinations were not done. Hypogammaglobulinemia, present in one patient, developed seven months before ocular disease appeared and replacement therapy did not alter the course of chorioretinitis. Leukopenia and neutropenia were present at the onset in Cases 2 and 3 but were intermittently present throughout and generally unrelated to disease activity.

Previous estimates of the prevalence of CMV chorioretinitis in immunosuppressed patients showed no disease in 80 pairs of adult eyes examined.[19] The three cases in 39 (7.7%) immunosuppressed patients excreting virus in their urine or saliva suggest the need to examine specific groups of immunosuppressed patients, determined by their experience with CMV infection, to estimate correctly the prevalence.

The failure of IDU and ara-A to provide any change in the disease in Cases 1 and 2 was striking and once begun, the progression of retinal disease was devastating and relentless. Since this disease continues for four to 11 months,[22,24] we cannot determine whether the apparently rapid rate of resolution after ara-A in Case 3 was due to therapy or was coincidental with natural recovery. The hematologic status of the leukemia produced no change in the progression of lesions and the disease continued throughout remission and into relapse. Early detection of chorioretinitis should be attempted by frequent ophthalmoscopic examination in immunosuppressed hosts with CMV infections, especially where viremia and tear excretion are present.

Summary

Cytomegalovirus (CMV) was recovered from the tears in eight of 41 (19.5%) children excreting CMV in their urine or saliva. Tear excretors were all immunosuppressed children with acute lymphocytic leukemia. Three had active CMV chorioretinitis and five did not develop retinal disease in nine to 15 months of observation. To our knowledge this was the first report of the recovery of CMV from tears and of acquired CMV chorioretinitis in children. One patient with active chorioretinitis presented with a disciform elevation of the macula. Therapy with adenine arabinoside (ara-A) or idoxuridine was ineffective in two patients while a third patient treated with ara-A possibly had a more rapid recovery. However, the significance is uncertain due to the unusual disease presentation and lack of data regarding the nature of cytomegalic inclusion disease chorioretinitis. Areas of retinal calcification were present at autopsy in one patient.

Acknowledgments

George J. Wyman, M.D., referred a patient. The ara-A was supplied by Lawrence Ch'ien, M.D., University of Alabama, Birmingham, Alabama.

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IMMUNOFLUORESCENT STUDIES OF OCULAR CICATRICIAL PEMPHIGOID

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Immunofluorescent studies of tissue and serum from patients with cicatricial pemphigoid initially failed to demonstrate characteristic staining reactions such as those occurring in pemphigus vulgaris and bullous pemphigoid.[1] Recent investigations, however, have documented that in persons with cicatricial pemphigoid, basement membrane zone deposition of immunoglobulins and complement occurs in skin, conjunctiva, and oral mucosa and is morphologically similar to that found in bullous pemphigoid.[2–7] Unlike bullous pemphigoid, however, circulating antibodies to the basement membrane zone are rarely detected.[1–10] We present the clinical and immunofluorescent histopathologic data from ten patients with chronic cicatricial conjunctivitis.

MATERIAL AND METHODS

The ten patients selected for study had cicatricial conjunctivitis which varied from mild to severe (Table 1). None had received oral corticosteroid or immunosuppressive therapy.

For direct immunofluorescent studies, we excised specimens of conjunctiva, oral mucosa, and skin from both involved and uninvolved sites. Ideally, biopsy specimens of both normal and diseased conjunctiva, oral mucous membrane, and skin would be taken from all patients. Only two patients, however, had buccal mucosal lesions and one had skin lesions. All patients had conjunctival lesions, but three patients had no normal conjunctiva (Fig. 1). Other patients with skin and buccal mucosal lesions without conjunctival lesions were not included in this study. Conjunctival specimens were taken when possible from areas of conjunctiva adjacent to erosions and scarring (Fig. 2). In patients with advanced disease, specimens were taken from scarred areas (Fig. 3). Buccal mucosal specimens were obtained from sites adjacent to erosions. A skin specimen was taken from the scalp lesion of the



Fig. 1 (Furey and associates). Case 1. Scarring bullous lesion of scalp and chronic scarring conjunctivitis.

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TABLE 1

CLINICAL INVOLVEMENT

Case No., Age, Sex	Visual Acuity*		Conjunctival† Scarring	Mouth Lesions	Skin Lesions
	R.E.	L.E.			
1, 60, M	20/50	20/200	+++	+	++
2, 64, F	CF	20/400	+++	−	−
3, 78, F	20/200	20/200	++	−	−
4, 22, F	20/20	20/20	+	+	−
5, 78, M	HM	HM	++	−	−
6, 58, F	20/200	20/200	+++	−	−
7, 56, M	20/40	20/40	++	−	−
8, 79, F	CF	20/200	+++	−	−
9, 62, M	CF	LP	+++	−	−
10, 73, F	20/50	20/40	++	−	−

* CF signifies counting fingers; HM, hand movement; and LP, light perception.
† +++ indicates severe scarring; ++, moderate scarring; and +, mild scarring.

patient with skin involvement (Fig. 1). Normal skin and buccal mucosa were obtained from all patients. The tissues were frozen in liquid nitrogen and stored at a temperature of −70°C. Sections 4 to 6 μ thick were cut in a cryostat at −20°C.

For indirect immunofluorescent studies, we used the following substrates: the patient's conjunctiva, buccal mucosa, and skin; guinea pig lip; mouse liver; and seborrheic keratosis (human skin). The controls were phosphate-buffered saline, normal human serum, bullous pemphigoid serum, and antinuclear antibody containing serum.

Standard direct and indirect immunofluorescent staining procedures were used to test all specimens.[10] We used commercially prepared fluorescein conjugated goat anti-human globulin (Igg), and IgG, IgA, IgM, IgD, and C_3 globulin. We used the following molar fluorescein to protein ratio (F/P) and antibody concentration of the conjugates and dilutions: IgG, F/P ratio 4.1, 0.8 mg antibody/ml diluted to a concentration of 40 μg/ml; IgA, F/P ratio 3.2, 0.8 mg antibody/ml diluted to a concentration of 40 μg/ml; IgM, F/P ratio 3.4, 1.2 mg antibody/ml diluted to a concentration of 60 μg/ml; IgD, F/P ratio 3.2, 0.5 mg antibody/ml diluted to a concentration of 50

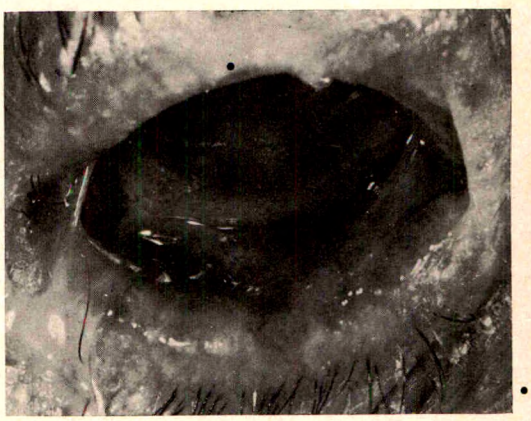


Fig. 3 (Furey and associates). Case 2. Severe conjunctival scarring with symblepharon formation, trichiasis, and corneal scarring with vascularization.

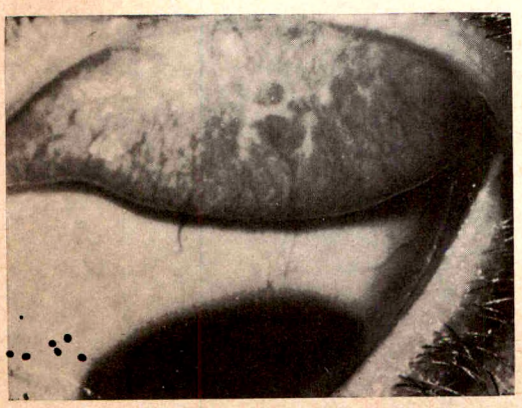


Fig. 2 (Furey and associates). Case 4. Mild, early, superficial scarring of upper tarsus.

TABLE 2

RESULTS OF IMMUNOFLUORESCENCE

Case No.*	Conjunctiva		Buccal Mucosa		Skin	
	Normal	Lesion	Normal	Lesion	Normal	Lesion
1		—	—	BMZ Igg, IgA	—	BMZ IgG, IgA
2		BMZ Igg,‡ IgG	—		—	
3	—	BMZ Igg	—		—	
4		BMZ Igg, IgG	—		—	
5†		—	—		—	
6	—	—	—		—	
7†	—	—	—		—	
8		—	—		—	
9		—	—		—	
10		—	—		—	

* Numbers correspond to Table 1.
† Positive antinuclear antibodies.
‡ Basement membrane zone antihuman globulin.

μg/ml; and C_3, F/P ratio 4.0, 0.5 mg antibody/ml diluted to a concentration of 50 μg/ml.

RESULTS

Direct immunofluorescent studies—Four of the ten patients had basement membrane zone deposition of IgG or IgA (Table 2). Three of the four patients (Cases 2-4) had conjunctival basement membrane zone staining (Figs. 4 and 5). One of these patients (Case 4) had clinical disease of the mouth and eyes; the other two had eye lesions only. The patient with eye, mouth, and skin in-

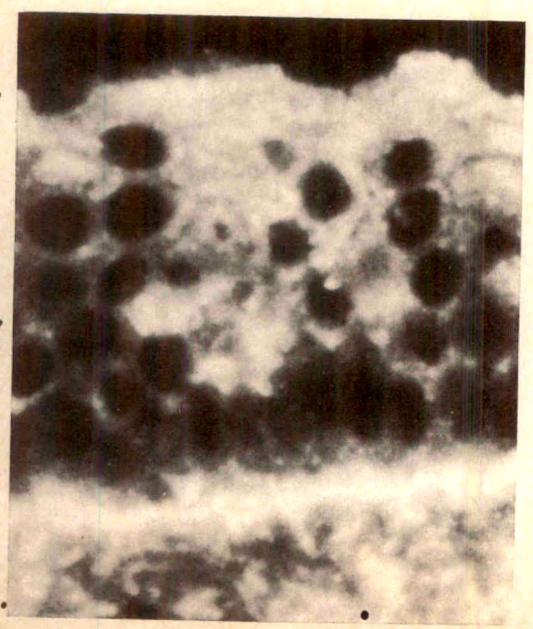


Fig. 4 (Furey and associates). Case 2. Direct immunofluorescence shows linear deposition of IgG along basement membrane zone of conjunctiva (×500).

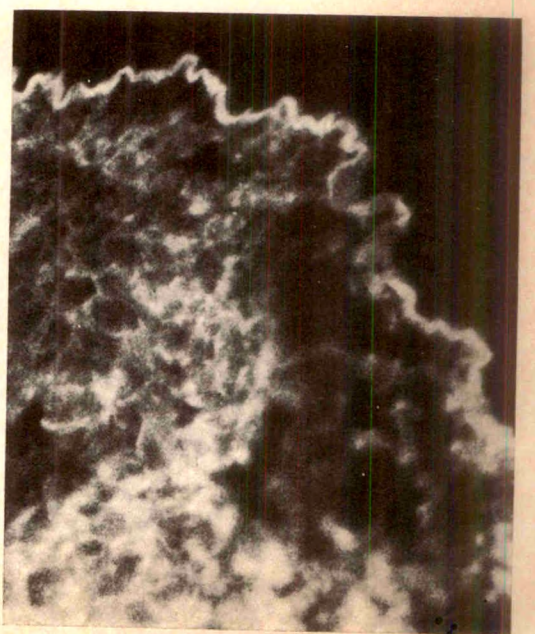


Fig. 5 (Furey and associates). Case 4. Direct immunofluorescence shows linear deposition of IgG along basement membrane zone of conjunctiva (×500).

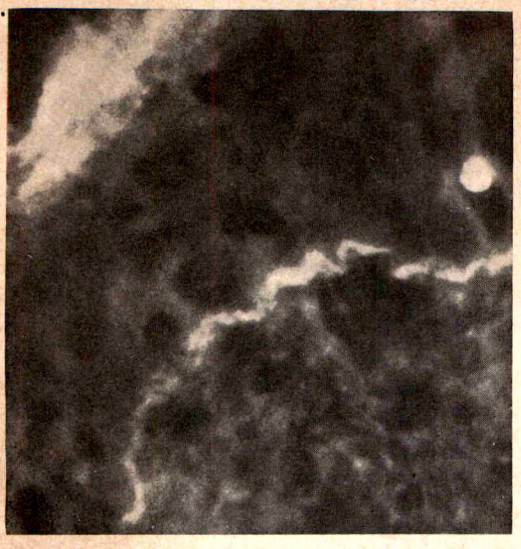


Fig. 6 (Furey and associates). Case 1. Direct immunofluorescence shows linear deposition of immunoglobulin at basement membrane zone of buccal mucosa (×500).

volvement (Case 1) (Fig. 1) had no conjunctival staining, but clinically involved buccal mucosa and skin showed basement membrane zone staining (Fig. 6).

Indirect immunofluorescent studies—We performed indirect immunofluorescent studies on all patients by using guinea pig lip and human skin as well as their own tissue as substrate. Circulating basement membrane zone antibodies were demonstrated in only two patients. In one (Case 2), circulating antibodies of IgG were bound to the basement membrane zone of the patient's normal skin. In the other (Case 1), circulating IgA antibodies were bound to the patient's normal buccal mucosa. No circulating antibodies were detected when their sera were incubated with guinea pig lip or homologous human tissue (seborrheic keratosis). Antinuclear antibody staining was observed in two patients at a 1:10 dilution, using their normal skin as a substrate; all sera were negative at 1:10 dilution, using mouse liver.

Discussion

The patients selected for this study had chronic cicatricial conjunctivitis.[11] In the evaluation of patients with chronic cicatricial conjunctivitis, we considered the following differential diagnoses of ocular scarring diseases: (1) old membranous conjunctivitis (diphtheria, beta-hemolytic streptococcus, adenovirus, primary herpes simplex); (2) trachoma; (3) trauma or surgery; (4) chemical burns; (5) erythema multiforme; and (6) pemphigus vulgaris. Bacterial or viral infections, although possibly complicating factors, could not alone be incriminated. When organisms were cultured and eradicated by appropriate therapy, the ongoing erosions and scarring persisted and progressed. The conjunctivitis of trachoma resembles the conjunctivitis of cicatricial pemphigoid in late stages, but the scarring of trachoma usually starts on the upper tarsus and superior fornix; a superior pannus descends over the cornea in an orderly fashion, and routine Giemsa-stained scrapings may demonstrate inclusion bodies. Pemphigus vulgaris may be associated with conjunctivitis, but a generalized acantholytic intraepidermal bullous eruption is usually present and scarring is a rare complication. Erythema multiforme is an acute process and resolves with appropriate therapy. It commonly leaves scarred conjunctiva, but there is no progressive scarring once the acute stage has subsided. Many patients had keratitis sicca; however, this is commonly associated with and secondary to conjunctival scarring regardless of etiology. The possibility that clinical scarring was aggravated by chronic allergic sensitization or irritant reaction to chemicals could not be definitely assessed. Many of these patients had used numerous proprietary and prescription ophthalmic preparations before being seen in the clinic. We diagnosed cicatricial pemphigoid of the eye by excluding other causes known to result in superficial and deep scarring of the conjunctiva with symblepharon formation, trichiasis, entropion, and keratitis sicca.

Cicatricial pemphigoid is a chronic blistering disease with a propensity to involve the

mucous membranes. Approximately three fourths of patients have ocular or oral involvement; one fourth have skin lesions.[1] Other less common sites include nasal, laryngeal, anal, and esophageal mucosa. In an attempt to further define this group of patients who were thought to have cicatricial pemphigoid, immunohistologic studies were performed on specimens from the conjunctiva, buccal mucosa, and skin.

In 1972, Bean and associates[2] reported the presence of basement membrane zone deposition of immunoglobulin in the conjunctiva, buccal mucosa, and skin specimens of two patients. These findings were confirmed by other investigators and are now considered characteristic of cicatricial pemphigoid.[3-6,12] However, most reported specimens have been from oral mucosa and skin. Positive basement membrane zone staining of the conjunctiva was reported by Griffith and associates[5] in one of two specimens, and by Cram, Griffith, and Fukuyama[7] in one specimen. In the present study, three of ten conjunctival specimens had immunoglobulin deposition in a linear pattern at the basement membrane zone. These specimens were obtained from two patients with no extraocular lesions. The other positive specimen was from a young woman with mouth lesions who had only mild superficial conjunctival scarring. The absence of conjunctival staining in the patient with immunohistologically positive mouth and skin lesions demonstrates that conjunctival staining may be absent in the presence of active disease. The absence of staining does not negate the diagnosis, but a positive staining reaction confirms the clinical impression.

Pemphigus vulgaris is another disease involving the eyes in which immunohistology of conjunctival biopsy specimens has been useful as a diagnostic aid. Bean, Holubar, and Gillett[13] reported a patient with widespread skin and mucous membrane acantholytic intraepithelial bullae who also had conjunctivitis. A conjunctival biopsy revealed the presence of typical intercellular staining, characteristic of pemphigus vulgaris.

Circulating epithelial antibodies in the serum of patients with cicatricial pemphigoid have rarely been demonstrated; it has been established, however, that sera from some patients have circulating basement membrane zone antibodies. Dantzig,[4] using rabbit esophagus as a substrate, reported circulating basement membrane zone antibody in a patient with mouth and widespread skin lesions. Bean[14] reported one patient with eye, mouth, and skin lesions with circulating antibody that bound to human skin and monkey esophagus. Two of his patients with conjunctival and oral lesions had serum antibody that did not fix to monkey, guinea pig, or human tissues, but did bind to their own skin and oral mucosa. Recently, Dabelsteen and associates[12] reported more circulating basement membrane zone antibody (seven of eight patients) using a double-layer technique. Using routine and double-layer indirect techniques, as well as guinea pig lip, monkey esophagus, and homologous human buccal mucosa as substrates, Griffith and associates[5] were unable to demonstrate circulating basement membrane zone antibody in 12 patients with oral lesions, three of whom also had ocular lesions. Hardy and associates[1] reported 15 patients with cicatricial pemphigoid who had no detectable circulating antibody. In this study, two patients had circulating antibody. One of these patients, with tissue-bound antibody in his oral mucosal and skin lesions, also had circulating antibody that bound to his own normal buccal mucosa, which had been previously examined and did not stain. The other patient with tissue-fixed conjunctival antibody had circulating antibody that bound to her unaffected skin, but not to her buccal mucosa. None of the sera had antibody that bound to guinea pig lip or to homologous human tissue.

This difficulty in detecting circulating basement membrane zone antibody is probably due to several factors: (1) The specificity of the antibody may be such that it is not

readily detected on the most widely used substrates. Chorzelski and Beutner[15] reported wide variations in the spectrum of specificities of the basement membrane zone antibody in bullous pemphigoid. Some bullous pemphigoid sera they tested gave positive reactions with monkey skin and mucosa but failed to react with rabbit and guinea pig tissue. In one case, the serum reacted only with normal skin. They concluded that antibody specificity may account for the 30% of cases of bullous pemphigoid in which circulating basement membrane zone antibody cannot be detected. (2) The avidity of fixation of circulating antibody to autologous basement membrane may also prevent detection of small amounts of unbound antibody by current immunofluorescent methods. (3) The antibody level may correlate with the extent of clinical involvement, that is, antibody will be most easily detected in those patients with widespread mucous membrane and cutaneous lesions.

Circulating antinuclear antibodies have also been found in the sera of patients with cicatricial pemphigoid. Peck and associates[8] reported positive antinuclear factor in two patients; Holubar, Honigsman, and Wolf[3] reported positive antinuclear factor in two of five patients tested. Waltman and Yarian,[16] using mouse liver substrate, found circulating antinuclear factor in 11 of 17 patients with cicatricial pemphigoid involving the eyes only. None of the 15 sera examined by Bean[17] showed nuclear staining. Two of the ten sera in this study showed antinuclear staining using autologous skin as a substrate, but none were positive with guinea pig lip or mouse liver. The significance of these findings is unknown because of the alteration of the immune state that occurs with the biologic process of aging. Most patients with cicatricial pemphigoid who have been studied are over 60 years of age, and there is more antinuclear antibody in the sera of the elderly.[18,19] But in cicatricial pemphigoid, where autoimmune factors may be playing a role in the process of tissue destruction, the finding of other tissue antibody would not be surprising.

A comparison of the clinical, histologic, and immunofluorescent findings in bullous and cicatricial pemphigoid reveals similarities. Both diseases are characterized by bullae; cicatricial pemphigoid has a greater propensity for mucous membranes and more severe local tissue destruction that may result in scarring. The histologic site of blister formation is the same, with subepithelial separation of skin and mucous membranes. Immunofluorescent staining shows immunoglobulin deposition along the basement membrane zone in both diseases. Unlike bullous pemphigoid, however, circulating antibody in cicatricial pemphigoid is more difficult to demonstrate. It may be that these two entities have the same pathogenic mechanism, but represent opposite ends of the spectrum. An analogous situation is found in lupus erythematosus. Severe scarring and local tissue destruction occur in discoid lupus erythematosus, in contrast to the more generalized tissue reaction seen in systemic lupus erythematosus, with more detectable circulating antibody to a variety of tissue antigens.

We hope additional immunologic data will shed new light on the role of autoimmunity in this devastating disease of the eye. At present, however, immunofluorescence can be useful as a diagnostic histologic technique to help identify patients with cicatricial pemphigoid and distinguish them from patients with other chronic scarring conditions of the conjunctiva.

Summary

Using direct and indirect immunofluorescent techniques, we studied ten patients with cicatricial pemphigoid (chronic cicatricial conjunctivitis). Serologic and histologic evaluation of 13 conjunctival, 12 mucous membrane, and 11 skin specimens from the ten patients showed that three had immunoglobulin deposition at the basement membrane zone of the conjunctiva. One pa-

tient had immunoglobulin deposited in the affected skin and oral mucosa. Two patients had circulating basement membrane zone antibodies that bound to their own tissue but not to guinea pig lip or human skin.

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NEUROLOGIC COMPLICATIONS WITH ELEVATED ANTIBODY TITER AFTER ACUTE HEMORRHAGIC CONJUNCTIVITIS

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Kono and associates[1] recently reported on the serologic confirmation of neurologic complications associated with acute hemorrhagic conjunctivitis (AHC) viral infection. They tested single sera from patients with histories of both AHC and neurologic complications. The sera were obtained from these patients one to 19 months after onset of AHC infection. They reported that a neutralization titer of $\geq$ 1:16 is of diagnostic value for AHC viral infection and that five of 11 sera obtained 14 to 21 months after onset from patients with histories of AHC alone had titers of $\geq$ 1:16 compared with the J-670/71 strain of AHC virus. In addition, the sera of eight of nine patients with histories of AHC and neurologic complications neutralized the J-670/71 virus strain to titers of $\geq$ 1:16 and as high as 1:512. Another group of patients with no history of AHC infection showed serum neutralization titers of $\leq$ 1:4.

We recently studied nine patients who developed neurologic complications after AHC infection, and obtained results similar to those reported by Kono and associates.[1] In addition one of the patients developed neurologic signs and symptoms early enough after the onset of AHC infection so that a significant rise in antibody titer could be demonstrated between the acute and convalescent sera of the patient. We present the serologic results on the nine patients who developed polyradiculomyeloneuropathy after AHC infection. We believe it is the first report demonstrating a significant rise in titer against AHC virus in a patient after the onset of paralysis.

MATERIAL AND METHODS

Cell line—HeLa-229 cells were grown in Eagle's minimal essential medium containing 10% fetal calf serum, 100 μ of penicillin, 100 μg of streptomycin, and 25 units of nystatin (Mycostatin) per milliliter. The maintenance medium used for inoculated cultures contained only 2% fetal calf serum.

Test antigens—Acute hemorrhagic conjunctivitis viral antigens used in the Tissue Culture neutralization tests (TCNT) were the J-670/71 strain isolated in Japan and I-13476/73, a strain isolated by our laboratory from a sample obtained from a patient in Indonesia.

Neutralization tests—Tissue culture neutralization tests were conducted using twofold dilutions in minimal essential medium of the patients' heat inactivated acute and convalescent sera mixed with an equal volume of test antigen containing 100 $TCID_{50}$ per 0.1 ml and allowed to interact for one hour at room temperature before inoculation of the cell cultures. Three tubes were inoculated with each serum dilution-viral mixture. The tubes were incubated at 35°C in a horizontal stationary position and examined over a period of seven days for

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

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† Deceased.

cytopathic effects. Virus and serum controls were included in the tests to insure that the proper amount of virus had been used and that the sera were not toxic. Titers were read as the highest dilution of serum inhibiting the cytopathic effects induced by the virus.

Results

Neutralization test results on sera from the nine patients who developed neurologic complications after AHC infection were studied. In addition the sera from two other patients with paralysis unrelated to AHC were tested blindly by the laboratory along with the sera from the AHC-neurologically complicated patients. The titers of these two pairs of sera were $\leq$ 1:4.

Almost all of the sera were obtained from patients one to two months after AHC infection and a second sample eight to 22 days later (Table). One patient (Case 1) developed AHC on July 23, 1974, and motor weakness began on July 28. Acute and convalescent sera were obtained from this patient on Aug. 5 and 16. Using these sera and the J-670/71 AHC virus strain as antigen, a fourfold rise in neutralization titer, from 1:16 to 1:64, was demonstrated. When tests of the sera from all patients were repeated using I-13476/73 and were only 36% related to the J-670/71 strain by cross-neutralization tests, a fourfold rise in titer from 1:8 to 1:32 still was demonstrated in their patient. Generally, the neutralization titers using the I-13476/73 virus strain were much lower than tests performed with the J-670/71 strain. Eighty-nine percent of the sera tested with the J-670/71 strain showed a titer of $\geq$ 1:16, while only 33% of the sera tested with the I-13476/73 strain had such titers.

TABLE

TCNT titers of sera from patients with polyradiculomyeloneuropathy after AHC infection*

Case No.	Antigen†	Onset of AHC	Date of Onset of Motor Weakness	Serum Titers			Date Drawn
				Serum 1	Date Drawn	Serum 2	
1	1	7-23-74	7-28-74	16	8-5-74	64	8-16-74
	2			8		32	
2	1	6-16-74	7-3-74	16	8-5-74	8	8-27-74
	2			< 4		4	
3	1	5-30-74	7-5-74	>32	8-5-74	128	8-13-74
	2			16		32	
4	1	6-25-74	7-2-74	32	8-5-74	16	8-16-74
	2			4		<4	
5	1	7-3-74	7-16-74	>32	8-2-74	64	8-13-74
	2			16		16	
6‡	1			< 4	8-8-74	<4	8-22-74
	2			< 4		<4	
7	1	7-30-74	8-10-74	8	8-16-74	8	9-2-74
	2			< 4		4	
8	1	7-11-74	8-9-74	32	8-22-74	32	9-2-74
	2			4		8	
9	1			4	8-27-74	<4	9-9-74
	2			<4		<4	
10	1	8-15-74	9-2-74	16	10-26-74	16	11-8-74
	2			< 4		<4	
11	1	8-5-74	8-12-74	>32	10-28-74	T	11-14-74
	2			8		T	

* Titers expressed as the reciprocal of the initial serum dilution; T indicates serum was toxic to cells.
† Antigen 1, J-670/71; antigen 2, I-13476/73.
‡ Patient with atypical paralysis not associated with AHC infection.

Discussion

We believe these results demonstrate the first significant fourfold rise in serum neutralization titer in a patient developing neurologic complications after AHC viral infection. In addition these results confirm the findings of Kono and associates[1] that neutralization titers of $\geq$ 1:16 in a single serum of patients suspected of AHC viral infection or its neurological complications, or both, are of diagnostic value.

In a study of seven AHC virus strains isolated between 1970 and 1972, Higgins and associates[2] showed that these strains could be divided into two serologically distinct groups. One group, consisting of Singapore/70 virus and the HK-3751/71 virus, was shown to cause paralysis in suckling mice. The cross-neutralization studies of one of us (I.J.G.) on AHC virus strains isolated between 1970 and 1973 from Singapore, Hong Kong, Taiwan, Japan, Morocco, and Indonesia suggest that these strains may be divided into three or four serologically distinct groups. These and our results indicate the importance of using the most appropriate or several different AHC virus strains to detect antibodies in the sera of AHC patients.

Kono and associates[3] have shown that the J-670/71 AHC virus strain is capable of producing paralysis in monkeys when inoculated simultaneously into the spinal cord and thalamus. Our demonstration of a fourfold rise in antibody titer against the J-670/71 strain in the serum of a patient who developed paralysis five days after the onset of AHC strongly suggests that this virus or one closely related to it was the etiologic agent. The most formidable evidence for such a relationship would be the isolation of such a virus from a patient with paralysis and the demonstration of a fourfold or greater rise in titer to the isolate, but, as Kono and associates[3] have reported, they were unable to reisolate the virus from inoculated monkeys after the onset of paralysis.

Summary

Nine patients with polyradiculomyeloneuropathy after acute hemorrhagic conjunctivitis (AHC) infection were studied serologically. All except one patient had neutralization titers $\geq$ 1:16 against the prototype J-670/71 strain of AHC virus in at least one of their serum samples. The development of a significant fourfold rise in antibody titer against AHC virus occurred in one of the patients who developed neurologic complications five days after the onset of AHC infection.

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INADVERTENT INJECTION OF CORTICOSTEROID INTO THE CHOROIDAL VASCULATURE

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Subconjunctival or subtenon's injection of depot corticosteroids as a convenient method of drug administration has acquired popularity in recent years. The more common indications include episcleritis, uveitis, pseudotumor, endocrine exophthalmos, and management of anticipated inflammation in anterior segment surgical cases. Judging from published reports,[1-5] the incidence of serious complications associated with the technique has been low; however, a definite and obvious risk of ocular perforation exists and must be taken into account in assessing the therapeutic index. I describe an unusual, perhaps unique, complication associated with an intended subtenon's injection of methylprednisolone acetate aqueous suspension (Depo-Medrol).

CASE REPORT

A 21-year-old white woman with a diagnosis of bilateral pars planitis for four years had increased inflammatory response on June 20, 1974. Except for varying amounts of inflammatory reaction in the inferior vitreous, involvement of other ocular structures had previously remained minimal. The recent exacerbation prompted institution of subtenon's injections of methylprednisolone. Visual acuity was 20/20 in both eyes before treatment and the anterior chambers were without cells or flare. Both irides were normal and the lenses were clear. The anterior vitreous body in both eyes contained inflammatory cells, aggregates of cells in vitreous opacities, and dense condensations overlying the pars plana inferiorly. The remainder of the ophthalmoscopic examination including the optic nerves, maculae, and retinal vasculature was normal. The injection technique, as described by her ophthalmologist, was as follows: after instillation of topically applied proparacaine, the patient was instructed to maintain upgaze as a mixture of 0.4 ml of methylprednisolone and 0.1 ml of lidocaine with epinephrine was injected in the subtenon's space near the 6 o'clock meridian by using a 30-gauge, 1.25-cm disposable needle, introduced approximately 8 mm from the corneoscleral limbus. The injection was uneventful. An identical technique was used for the right eye; however, most of the injected material refluxed around the injection site, necessitating reinjection. The repeat injection was accompanied by marked pain and subtenon's hemorrhage. The ophthalmologist stated that there had been no unusual resistance to passage of the needle or resistance to the injection. The patient's distress precluded a detailed ocular examination; however, cursory examination revealed white, flocculent material in the anterior chamber. Twenty-four hours after the injection incident, the patient was reexamined by her ophthalmologist and had the following findings: visual acuity was R.E.: 20/40, and L.E.: 20/20, with a subtenon's hemorrhage inferiorly, a moderate number of cells in the anterior chamber, intraocular pressure of 10 mm Hg by applanation tonometry, and flocculent material settled on the iris surface. Ophthalmoscopic examination documented the presence of similar material within the major choroidal vasculature inferiorly extending posteriorly and superiorly (Figure). No choroidal or retinal damage could be seen in the meridian of the injection site. Seven days after injection, the anterior chamber was clear and most of the injected material had cleared from the choroidal vasculature of the right eye.

Three weeks after the injection I examined the patient. A resolving subconjunctival hemorrhage was evident in the right eye inferiorly. Pupillary light responses and extraocular movements were normal. Visual acuity was R.E: 20/25, and L.E.: 20/20. The biomicroscopic examination revealed normal corneas, anterior chambers, irides, and lenses. There were cells in both anterior vitreous bodies inferiorly. Ophthalmoscopic examination of the right eye revealed a moderate amount of opacification within the vitreous body overlying the inferior pars plana. Several choroidal vessels in the posterior pole still demonstrated small segments containing material presumed to be residual corticosteroid. The peripheral fundus was visible and no evidence of choroidal damage, retinal pigment epithelial reaction, or retinal perforation was found. Ophthalmoscopic examination of the left eye showed opacities overlying the inferior pars plana as in the right eye. Two months after injection, acuity was R.E.: 20/20, and no apparent intraocular damage was evi-

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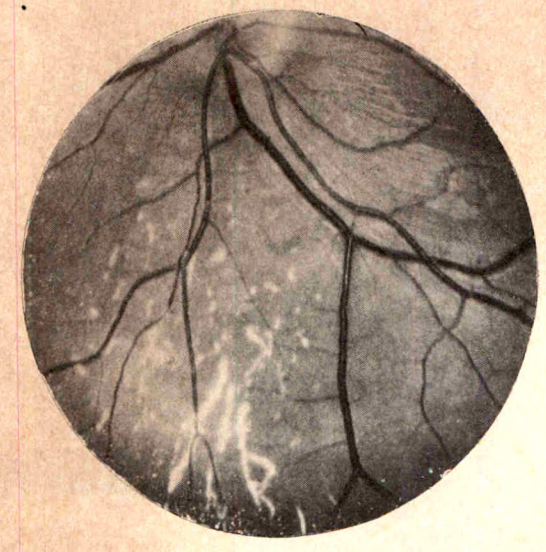


Figure (McLean). Depot corticosteroid material within choroidal vasculature 24 hours after inadvertent intraocular injection.

dent. The chronic findings due to pars planitis appeared to be unchanged.

Discussion

In this patient, choroidal intravascular corticosteroid injection resulted from inadvertent cannulation of an intrascleral or extrascleral vortex vein. With the globe in supraduction the exit sites of the inferior vortices are correspondingly rotated anteriorly, in proximity to the injection needle. In addition, the veins are under longitudinal traction with the rotation, and are relatively fixed in position by episcleral adventitia at the exit site. Given these anatomic considerations, inadvertent cannulation and injection of a vortex vein could occur. This explanation is hypothetical and does not constitute proof of the mechanism for the complication.

Although most periocular injections are uncomplicated, there is an undeniable risk with each injection. Schlaegel[1] reported the advantages and disadvantages in his observations on 4,000 subtenon's injections without complication and, in contrast, a collected series of six cases in which inadvertent intraocular injection of depot corticosteroid resulted in four cases of legal blindness.[6] The incidence of complications may be inferred from these series; however, it is unlikely that the true incidence will ever be determined. The risk of incurring a complication exists with every injection and one should not become complacent with the seemingly reassuring low incidence data from these series.

An increased awareness of the complications may be helpful in avoiding inadvertent intraocular injections; however, even with reasonable care most ophthalmologists have been completely unaware of the perforations when they occurred. The prevention lies in modifying the technique. Nozik[3] noted that techniques of injection without direct visualization of the needle tip probably carry the highest risk of intraocular perforation, and Ellis[4] cited this practice as one of several possible contributing factors. Giles[5] recommended direct visualization of the needle tip as it is passed into the subtenon's space before injection. Observance of this modification should help to eliminate accidental perforation of the globe and associated intraocular complications.

Summary

A 21-year-old woman with pars planitis was treated with a subtenon's depot corticosteroid injection that was complicated by the appearance of the corticosteroid suspension within the choroidal vasculature. White, flocculent material was observed in the anterior chamber and 24 hours later this settled on the iris surface. Similar material was located in the major choroidal vessels. Two months after the incident, the choroid was normal appearing but the pars planitis was unchanged.

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Ophthalmic miniature

From 1968 to 1974 the number of total students enrolled in American medical schools increased from 35,833 to 53,554. The number of new medical schools similarly increased from 86 in 1961 to 114 in 1973-1974. As a result of this activity, the number of entering medical students in 1971 exceeded the Carnegie Commission's most optimistic projection by 961, with the goal of 15,000 first-year medical students in the academic year 1976, set by the Association of American Medical Colleges in 1971, probably being realized by 1975. The number of graduating medical students increased from 7574 in 1966 to 11,862 in 1974, which is 862 more graduates than recommended by the Bane Report in 1959 as the number of graduating students needed by 1975 to maintain the then prevailing physician-population ratio. These changes have resulted in a net increase in the physician population of 3 per cent per year as compared to a 1 per cent annual increase in the general population, raising the number of active nonfederal physicians per 100,000 population from 119 in 1950 to 152 in 1971.

Barry Stimmel, Congress and health manpower: A legislative morass
N. Engl. J. Med. 293:69, 1975

SURGICAL REMOVAL OF NONMAGNETIC FOREIGN BODIES

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Ocular perforating injuries from retained nonmagnetic foreign bodies in the posterior segment usually result in extensive ocular damage and often culminate in a poor visual outcome.[1-3] The removal of the foreign body itself has complications. Although the use of the ultrasonic foreign body forceps has improved the extraction rate, visual results are ultimately poor.[2] Earlier surgery, using newer techniques, appears to improve the visual outcome.

We used an improved technique to remove nonmagnetic foreign bodies in the posterior segment. The procedure combines a pars plana location for introduction of the foreign body forceps with an operating microscope and corneal contact lens. Vitrectomy is employed in most cases.

There are several advantages to this surgical approach. The superior viewing system afforded by the operating microscope allows controlled intraocular maneuvers. The removal of opacities and abnormalities of the ocular media by vitrectomy offers unobstructed visualization of the foreign body. The surgical assistant can enter fully into the operation, thereby allowing the surgeon to use both hands for intraocular maneuvers. Therefore, it is possible to use the foreign body forceps and the vitreous cutter simultaneously. This latter maneuver allows removal of encapsulated foreign bodies without producing large retinal tears or extensive retinal destruction.

MATERIAL AND METHODS

Foreign body extraction without vitrectomy—Much of the ancillary equipment for vitrectomy, as described by Machemer,[4] can be used to considerable advantage in any intraocular manipulation; therefore, we incorporated these devices into our technique. We used a plastic drape positioned to allow drainage of excess saline into a trough around the head where a suction apparatus removed the fluid. This arrangement was similar to the one recently described by Machemer and Uffenorde.[5] A wire eyelid speculum was used to retract the eyelids and 4-0 silk sutures were placed transconjunctivally under the four rectus muscles to act as traction sutures. An armrest surrounded the patient's head and was valuable as an aid to relaxed, controlled intraocular maneuvers.

The sclerotomy site was usually located in a quadrant other than that occupied by the foreign body, and was positioned so that the tract of the foreign body forceps did not pass through the visual axis. A radial conjunctival incision was made over the proposed sclerotomy site. After cauterization of episcleral vessels, a sclerotomy site, 3 mm long, was prepared parallel to and 4.5 to 5 mm from the corneoscleral limbus (Fig. 1, bottom). A Beaver blade (No. 64) was used to produce a superficial scleral incision. This incision was surrounded by a 5-0 dermalon suture placed as a mattress suture. We completed the incision into the vitreous cavity by using a 1.9-mm sclerotomy knife designed for posterior vitrectomy (Fig. 1, top), and entering perpendicular to the sclera to avoid lens damage. Neither cryotherapy nor diathermy was applied to the sclerotomy site before entering the eye. After removing the sclerotomy knife, the surgeon introduced the foreign body forceps through the sclerotomy while the surgeon and assistant held open the lips of the incision. We preferred the Neubauer foreign body forceps (Fig. 2) because of the small shaft size, excellent grasping facility, and

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squeeze handle. The oval cupped, squeeze-handled forceps were used for shot pellets.

When the forceps are introduced into the vitreous cavity, the peripheral retina or ciliary body must not be detached. After we introduced the foreign body forceps, we placed a flat contact lens equipped with a constant infusion on the cornea. We used the Zeiss operating microscope, with coaxial illumination, zoom magnification, binocular assistant observer's pieces, and XY movement, throughout the operation. The stability of the surgeon's position, coupled with the excellent stereoscopic visualization offered by the operating microscope, enabled controlled manipulations of the intraocular instruments close to the surface of the retina.

In most instances the foreign body was not located in the central vitreous or retina; therefore, the eye must be rotated to bring the object into view. The most effective way to rotate the eye was with the coordinated use of the foreign body forceps and the contact lens (Fig. 3). The forceps acted as a lever, by moving the eye to the desired position. Light pressure on the corneal contact lens then maintained the eye in the proper position. The forceps moved freely inside the eye with the sclerotomy acting as a fulcrum. Under the direct binocular viewing system provided by the operating microscope, the surgeon grasped and gently extracted the foreign body. The sclerotomy was closed by interrupted 6-0 dexon sutures and the preplaced mattress suture was then removed. The closure allowed scleral buckling procedures and if necessary, the use of intravitreal air or sulfur hexafluoride (SF_6). After the sclerotomy site was closed, we carefully examined the retina with the indirect ophthalmoscope and applied cryotherapy to

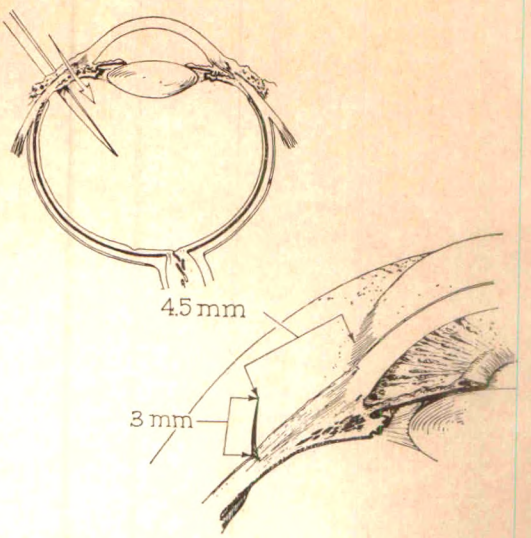


Fig. 1 (Hutton, Snyder, and Vaiser). Top, Sclerotomy knife enters prepared site, perpendicular to the sclera. Bottom, Detailed view of sclerotomy site.

the area around the sclerotomy site and to retinal areas damaged by the foreign body.

The basic technique for removal of nonmagnetic foreign bodies can be altered to control the various problems that develop; in particular, the problems of hypotony and hemorrhage. Hypotony decreases the maneuverability of the eye and increases the risks of intraocular maneuvers striking adjacent collapsing structures. Even with the careful introduction of the foreign body forceps coordinated with tightening of the sclerotomy suture, liquid or semisolid intraocular contents may escape. A simple method of restoring pressure is to introduce a 27-gauge needle attached to a 5-ml syringe filled with a balanced salt solution into the eye through the original sclerotomy site. After injecting the material, the needle is withdrawn. If a continuous leak develops, the



Fig. 2 (Hutton, Snyder, and Vaiser). Neubauer foreign body forceps.

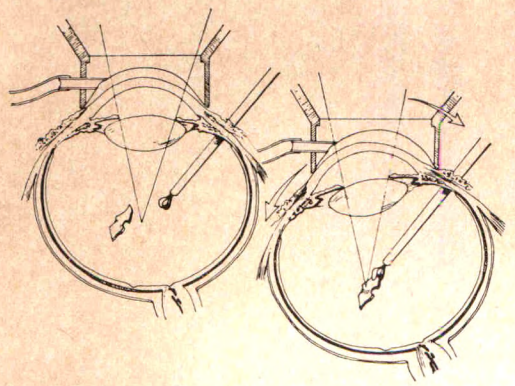


Fig. 3 (Hutton, Snyder, and Vaiser). Coordinated movements of foreign body forceps and contact lens rotate the eye to the desired location.

surgeon can introduce a 21-gauge needle through the pars plana, usually in a superior quadrant of the eye, but excluding the quadrant of the sclerotomy site. This needle is attached to a bottle of Ringer's solution for continuous minimal infusion while manipulations are performed. Since the surgeon's hands are manipulating the foreign body forceps and the 21-gauge needle, the assistant must hold the contact lens on the eye.

The removal of foreign body using vitrectomy—Indications for vitrectomy are vitreous hemorrhage, occurring either preoperatively or at the time of foreign body removal, and vitreous bands or organization predisposing to retinal detachment or interfering with extraction of the foreign body. Occasionally the nonmagnetic foreign body is dissected free by using a jet stream of infusion from a 21-gauge needle although vitrectomy is a superior way to free the foreign body. The vitreous machine is inserted through the same sclerotomy site as the foreign body forceps, and the vitrectomy performed. After removing the vitreous abnormalities and freeing the foreign body of all attachments, the vitreous cutter is removed and the foreign body forceps introduced.

A more effective way of removing the foreign body is the simultaneous use of the foreign body forceps and the vitreous suction cutter (Fig. 4). This technique is especially useful when the foreign body is encapsulated adjacent to the retina, or if there is a retinal detachment present. When two instruments are used, the sclerotomy sites are prepared in different quadrants, usually choosing a superotemporal and superonasal location. Preoperative localizing x-ray films or ultrasonography determine the position of the foreign body and from that information, the surgeon determines the proper location of the sclerotomy sites.

The assistant acts as a "third hand," not only activating suction, but also holding the corneal contact lens in place. This maneuver is difficult and should be mastered by the assistant and surgeon before attempting the delicate maneuvers necessary in the removal of the foreign bodies.

After introduction of both instruments into the vitreous cavity, we gently retracted the foreign body from the retinal surface using the foreign body forceps while the encapsulating tissue was nibbled away. As the foreign body was gradually freed of adhesions and retracted away from the retinal surface, we used the vitreous suction cutter to remove the vitreous membranes as they occurred. The vitrectomy probe

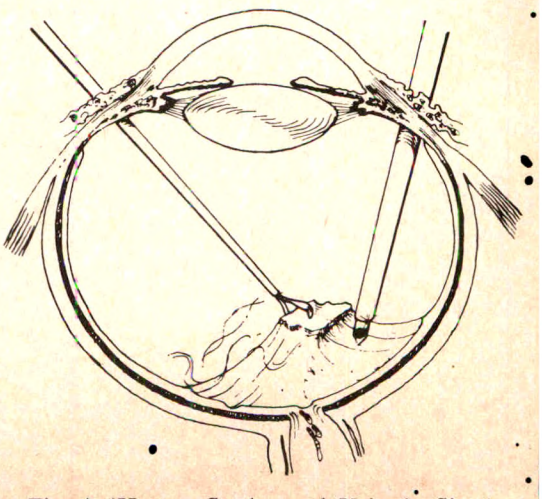


Fig. 4 (Hutton, Snyder, and Vaiser). Simultaneous use of foreign body forceps and vitrectomy machine.

equipped with the fiberoptics light provided excellent intraocular illumination. The simultaneous use of the two instruments in this manner increased the control of the foreign body, decreased the instances of large retinal tears, and lessened the likelihood of extensive retinal destruction.

The foreign body was occasionally enmeshed in organized vitreous fluid at the ora serrata. In these cases the assistant used a muscle hook to indent the sclera, thereby permitting visualization of the fragment (Fig. 5). The object was then grasped by the foreign body forceps and freed of attachments by the vitreous cutter. After removal of the foreign body the sclerotomy sites were closed.

Results

Using these methods we operated on seven patients with retained nonmagnetic foreign bodies from October 1973 through September 1974. The average follow-up time, as of March 1975, averaged 10.6 months. One patient was operated on by extraction of foreign body without associated vitrectomy. Initial visual acuity in this patient was 20/30 and remained so one year after surgery (Table 1). Of the six patients treated by vitrectomy five had improved visual acuity. Four patients had visual acuity better than 20/40. These four patients were all treated by vitrectomy and their foreign bodies were removed within three weeks of the initial injury.

TABLE 1

VISUAL RESULTS

Visual Acuity	No. of Patients	
	Before Operation	After Operation
20/20–20/40	1*	4
20/60–20/100		
20/200–20/400	1	2
CF	1	
HM	2	1
LP	2	

* Patient operated on by extraction of foreign body without vitrectomy.

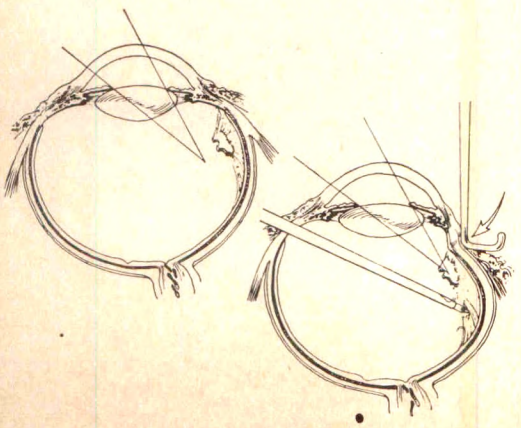


Fig. 5. (Hutton, Snyder, and Vaiser). Simultaneous use of scleral indentation and vitrectomy machine to remove peripherally located encapsulated particles.

Operative complications were infrequent (Table 2). A peripheral retinal tear was produced in one patient during extraction of an encapsulated brass foreign body attached to the inferior peripheral retina. The tear was recognized and treated by intravitreally administered SF_6 cryotherapy and an explant; final visual acuity was 20/30. Mechanical inability to cut a dense vitreous band forced us to use intravitreal scissors in one case with a long-standing encapsulated foreign body, vitreous band, and retinal detachment. The encapsulated foreign body was not removed in this case. Injury to an otherwise clear lens was always a possibility with intravitreal manipulation. Five of the seven patients had cataracts and these were removed through the pars plana by using the vitrectomy machine during the primary operation. No cataracts were produced in the two remaining lenses.

There were two immediate postoperative complications. A transient increase in intraocular pressure, secondary to the use of intravitreal sulfur hexafluoride, and an explant for retinal detachment responded to systemic acetazolamide. Persistent iritis de-

TABLE 2
COMPLICATIONS

	No. of Patients
Operative	
Retinal tear	1
Inadequate cutting by vitrectomy machine	1
Inability to remove foreign body	2
Postoperative	
Immediate	
Increased intraocular pressure (SF_6)	1
Iritis	1
Delayed	
Retinal detachment (one reattached)	2

veloped in a patient with a subretinal metallic (probably brass) nonmagnetic foreign body, retinal detachment, and corneal scleral laceration suffered four months before vitreous surgery. The ultimate outcome was redetachment of the retina with massive preretinal retraction.

In two patients, the major delayed complication was retinal detachment. The patient treated by extraction of the foreign body without vitrectomy developed a localized peripheral retinal detachment. It was repaired without impairment of visual acuity.

DISCUSSION

The removal of intraocular nonmagnetic foreign bodies is particularly difficult since the foreign body cannot be manipulated to a favorable position by indirect methods. The surgeon must localize, grasp, and remove the foreign body by using intraocular maneuvers. Problems may develop with visualization of the foreign body, inability to grasp and deliver the object, and inadvertent retinal tears or damage to other intraocular structures.

One common technique for removal of nonmagnetic foreign bodies involves the use of the indirect ophthalmoscope and foreign body forceps.[6] Although this method has the advantage of depth of focus and a large field of view, there are several inherent problems. The first is reversal of image field with the use of the indirect ophthalmoscope and condensing lens. In reality, however, most ophthalmologists handling foreign bodies are well acquainted with the indirect ophthalmoscope, and are accustomed to correcting for reversal of imagery. Additional disadvantages lie in the relatively poor magnification coupled with unsteadiness in manipulation of the eye. In an effort to coordinate the positioning of the condensing lens and the foreign body forceps, the surgeon in this suboptimal position may miscalculate the distance from the retina or other intraocular structures, a major problem when one is attempting to remove a foreign body from near the surface of the retina.

In most cases the foreign body is not visible because of a vitreous hemorrhage or cataract formation, or both. In these cases, the ultrasonically guided forceps are reported to give a good extraction rate, but unfortunately the visual results are poor.[2] With the availability of vitrectomy the essentially blind procedure using the ultrasound forceps is no longer indicated. The vitrectomy machine is used to remove the opaque media, thereby allowing direct, unobstructed visualization of the foreign body. Simultaneous use of the foreign body forceps and vitreous suction cutter equipped with fiberoptics offers a controlled, effective method for removing encapsulated particles without producing extensive retinal destruction.

Our experience with closed (transscleral) vitrectomy encouraged us to extend the ancillary instrumentation to nonmagnetic foreign bodies when vitrectomy was not required. Several of the techniques described here have been briefly reviewed by Machemer.[7] Most of the features we describe are modifications of the vitrectomy procedure.[4] The operating microscope provides stereoscopic vision, good magnification, and fine focus that determines the exact location of the foreign body referable to the intraocular

structures. Complete control of the intraocular instruments is mandatory. The armrest serves as a platform for the surgeon's arms, allowing the surgeon to relax. The eye position is stabilized by the action of the contact lens and foreign body forceps. All these factors allow the surgeon to manipulate the eye in any direction needed for clear visualization of the foreign body.

The assistant is particularly important and performs certain functions, such as holding the contact lens or using the muscle hook to indent the sclera. The surgeon is then able to use both hands for intraocular maneuvers.

An aggressive approach to penetrating injuries, especially those of nonmagnetic foreign bodies, seems mandatory considering the poor results reported by other authors.[1-3] One author[2] stated 13% of patients with nonmagnetic foreign bodies had 20/400 or better vision. Other authors reported uniformly poor results, and inoperable retinal detachments later developed after initially good results.[1] Many of these problems are now avoided by the use of vitrectomy combined with the excellent visualization afforded by the operating microscope. For example, a combination of vitreous hemorrhage and a foreign body is handled not by waiting but by immediate vitrectomy and a controlled removal of the foreign body. This more aggressive approach prevents encapsulation of the foreign body and avoids more extensive retinal trauma associated with uncontrolled extractions. Our preliminary series indicates an aggressive early approach to penetrating injuries in general, and nonmagnetic foreign bodies in particular, improves the salvage rate in these eyes, and prevents delayed complications of vitreous organization and inoperable retinal detachments.

Summary

A microsurgical technique for the removal of nonmagnetic foreign bodies in eyes with opaque media incorporated the simultaneous use of the foreign body forceps with a vitrectomy machine equipped with fiberoptics. The superb viewing system provided by the operating microscope combined with the excellent illumination from intraocular fiberoptics offered precise surgical control. Nonencapsulated nonmagnetic foreign bodies in eyes with clear vitreous cavities were removed by using the operating microscope, corneal contact lens, and foreign body forceps introduced through a pars plana location. Vitrectomy was not performed. The surgical techniques allowed early removal of the foreign body and, in a preliminary series of cases, improved visual results in what is usually a devastating ocular injury.

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THE REPRODUCIBILITY OF THE INTRAOCULAR PRESSURE RESPONSE TO DEXAMETHASONE

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The intraocular pressure response to topical corticosteroids has been studied by many investigators, but the reproducibility of the response has not been characterized adequately.[1-10] Since such an estimate of precision is important, we have studied the reproducibility of topical testing in 162 persons.

Corticosteroid-induced ocular hypertension originally attracted attention when it became apparent that it could fully mimic primary open-angle glaucoma. Soon after corticosteroid ocular anti-inflammatory therapy was introduced, François[11] and Goldmann[12] reported cases in which long-term use of corticosteroid eyedrops by susceptible persons inadvertently led to elevated intraocular pressure, decreased outflow facility, optic nerve-head cupping, and glaucomatous field loss.[13] Interest in the phenomenon increased when it was demonstrated that an increased pressure response to corticosteroid was closely associated with primary open-angle glaucoma.[3,14] Thus, while only 6% of a normal population responded to six weeks of dexamethasone testing with an intraocular pressure elevation to > 31 mm Hg, 82% of primary open-angle glaucoma patients responded in this fashion.[10]

When test results for normal volunteers, and for glaucoma patients, their siblings, and offspring, were analyzed by using cumulative frequency distribution plots, deviations from single Gaussian distributions were noted.[15-17] Becker[5] hypothesized that the observed skewed distribution of final pressures reflected an underlying trimodal distribution of low, intermediate, and high responses. These three phenotypes would represent the expression of corresponding Mendelian genotypes: homozygous nonresponders (low responders), designated NN; heterozygous (intermediate) responders, NG; and homozygous (high) responders, GG. To test the hypothesis, family studies were performed, and the results were impressively consistent with simple Mendelian inheritance.[18] Armaly[4,14,19] performed similar work using criteria of corticosteroid-induced change in pressure, rather than final pressure achieved, and obtained similar results.

The genetic hypothesis has been seriously challenged by the results of a study of corticosteroid response in twins.[20] Schwartz and co-workers[20] found only a 65% concordance of response by categories, using final pressure criteria, for 37 pairs of identical twins. The computed heritability index for ocular pressure response was 0.31, on a scale of 0 to 1, suggesting a limited role for inheritance. The authors of the twin study noted, however, that the precision of their assessment of the heritability of corticosteroid response depended upon the reproducibility of topical ocular testing. Unfortunately, there were no data available from which to estimate the replication error of topical testing. If the reproducibility of topical testing was proved to be excellent in other studies, then the discordance of results in identical twins would indeed be evidence that inheritance played but a small role in corticosteroid response. On the other hand the poor concordance of results in identical

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twins might only be indicative of a poor reproducibility of topical testing.

Another important aspect of the twin analysis is that it applies to a general population, one with few high corticosteroid responders. It is the high response state, however, which is of most interest because of its high association with primary open-angle glaucoma. Possibly, the large pressure response shown by high responders might dwarf competing influences upon intraocular pressure (diurnal pressure, state of hydration), and thus yield a considerably higher reproducibility for high responders than would be found for intermediate and low responders. Data on the reproducibility of topical testing were needed in order to clarify these matters.

Methods

Data on the reproducibility of topical testing were obtained for 89 persons (15 NN, 28 NG, and 46 GG) by retrospective analysis of the records of the Glaucoma Center at Washington University. A second test had been performed on these patients as part of various protocols, none of which influenced intraocular pressure response. An additional 73 patients, previously tested once (21 NN, 46 NG, and 6 GG), were retested expressly for this study. Both groups of patients included normal volunteers, ocular hypertensives, and siblings and offspring of glaucoma patients. None of the tested patients had primary open-angle glaucoma with visual field loss, and none were receiving ocular antihypertensive therapy in a tested eye. The sample included 59 white men, 14 black men, 57 white women, and 32 black women. The average age was 47.4 $\pm$ 16.4 (σ) years. The NN patients averaged 40.6 $\pm$ 18.6, the NG patients 49.8 $\pm$ 13.3, and the GG patients 47.4 $\pm$ 16.4 years.

All patients received a complete eye examination before testing. Refraction, external examination, motility testing, slit-lamp examination, applanation tonometry, tonography, gonioscopy, Goldmann kinetic perimetry, and a dilated fundus examination were performed on each patient. Patients with anatomically narrow anterior chamber angles, evidence of ocular inflammatory disease, or visual field loss were excluded.

Replicate testing was performed in three ways. One hundred fifty of the 162 patients had testing repeated on the same eye on different occasions, 86 had testing on opposite eyes on different occasions, and 73 had simultaneous bilateral testing.

After a baseline Goldmann applanation tonometer reading was taken, testing was begun with 0.1% dexamethasone-21-phosphate (Decadron), one drop four times daily, on an outpatient basis. Applanation pressures were determined at three and six weeks on frequently calibrated instruments by experienced technicians. In addition, those patients with elevated pressures at three weeks were often checked at intervals of one week during the last three weeks. Testing was frequently terminated when the pressure exceeded 31 mm Hg. The first test was stopped before six weeks for 32 of 52 GG responders. The second test was stopped for 26 of 56 GG responders. The interval between testing periods ranged from three weeks to six years, averaging 1.83 $\pm$ 1.57 years. In all cases intraocular pressure had returned to baseline before retesting.

No special assessment of patient compliance was attempted. Three patients were excluded from the reported group when they volunteered the information that they had missed taking drops for several days during the testing period. Twelve patients failed to return for final pressure readings. One patient was excluded because she developed postcorticosteroid uveitis (at the completion of both her second and third tests).[21] Patients were not paid for participating in this study.

The criteria of response were as follows:

Final pressure criteria:

Low response (NN)—final intraocular

TABLE 1

REPEAT TESTING OF THE SAME EYE ON DIFFERENT OCCASIONS

1st Test	2nd Test	All Tested	Initial IOP <20 mm Hg
NN	NN	22 (71%)	21 (72%)
NN	NG	9	8
NG	NN	6	3
NG	NG	52 (74%)	29 (76%)
NG	GG	12	6
GG	NN	1	0
GG	NG	9	1
GG	GG	39 (79%)	14 (93%)

pressure by applanation < 20 mm Hg at the end of six weeks' administration of 0.1% dexamethasone-21-phosphate eyedrops to one eye four times daily.

Intermediate response (NG)—final pressure 20 to 31 mm Hg.

High response (GG)—final pressure > 31 mm Hg.

Change in pressure criteria:*

Low response (pLpL)—rise in intraocular pressure by applanation < 6 mm Hg from the beginning to end of six weeks' administration of 0.1% dexamethasone-21-phosphate to one eye four times daily.

Intermediate (pLpH)—rise in pressure 6 to 15 mm Hg response.

High response (pHpH)—rise in pressure > 15 mm Hg.

RESULTS

Testing repeated on the same eye on different occasions—One hundred fifty patients had testing performed on the same eye on different occasions. The concordance of first and second test results by response category was 71% for NN, 74% for NG, and 79% for GG (Table 1).

The reproducibility of testing by category was compared to the concordance of test results that would be expected by chance (Table 2). If the results of second testing were dependent upon sheer chance, then the second test result would be independent of the first result, and would be distributed as in the general population (58% NN, 36% NG, and 6% GG).[10] The concordance of test results exceeded chance for all categories, and was statistically significantly greater for the NG and GG categories.

The results of repeat testing were used to estimate the reproducibility of topical testing in a general population. To do this the contribution of each category to the overall reproducibility was adjusted to correspond to its proportion of the general population (Table 3).[22] The reproducibility of topical testing in the general population was calculated to be 73%. Chance concordance would be 47%. The difference was significant ($P < .005$).*

Testing of opposite eyes on different occasions—Eighty-six patients had testing performed on opposite eyes on separate occasions (Table 4). The concordance of test results exceeded chance for all categories. The computed concordance for testing of opposite eyes in a general population was 73%.

Analysis by the change in pressure criteria—The results for repeat testing of the same eye are presented in Table 5. The concordance of test results exceeded chance for all categories, but was statistically significantly greater only for the pHpH category. The computed concordance for repeat testing in a general population was 61%. Chance concordance would be 52%, based on a general population[4] of 66% pLpL,

* For a six-week test rather than for four weeks as defined by Armaly, and using drops four times daily rather than three.

* By chi-square analysis, computed as follows: The sample size of the computed general population was based on the smallest component sample, NN. Thus sample size was (100%/58%) × 31 NN patients = 53 patients. With 73% concordant, there were computed to be 39 concordant, 14 discordant. Chance was taken from Becker's 300 patients[1,3] (58% NN, 36% NG, and 6% GG), of whom 47%, or 141 patients, would be concordant by chance. $\chi^2 = 12.7$.

TABLE 2

COMPARISON OF OBSERVED CONCORDANCE TO CHANCE

1st Test Category	Observed Concordance, %	Chance Concordance, %	χ^{2*}	P
NN	71	58	20	N.S.†
NG	74	36	34	$P < .0005$
GG	79	6	167	$P \ll .0005$

* Chi-square analysis. Compares observed concordant and discordant responses to those expected within each category by chance, using Becker's 300 patient sample of 124 NN, 108 NG, and 18 GG responders.[10]
† N.S. designates not significant.

29% pLpH, and 5% pHpH. The difference was not significant.

The results by change in pressure criteria for testing of opposite eyes on separate occasions are presented in Table 6. Again, concordance exceeded chance for all categories, but was significantly greater only for the pHpH category. The computed concordance for opposite eyes in a general population was 60%, which was not significantly greater than chance.

Quantitative assessment of the reproducibility of topical testing—The reproducibility of topical testing also was analyzed quantitatively. The final pressure achieved upon first testing was plotted against the final pressure achieved upon second testing of the same eye for 150 patients (Fig. 1). The correlation coefficient for regression analysis was .747, showing a significant correlation of results ($P < .001$).[23]

The change in pressure achieved on first testing was plotted against the change in pressure achieved upon second testing of the same eye for 150 patients (Fig. 2). The correlation coefficient for regression analysis was .598 ($P < .001$).

Direct comparison of the results of repeated single eye, opposite eye, and simultaneous bilateral testing—To provide the most valid comparison of repeated single eye, opposite eye, and simultaneous bilateral testing, analysis was limited to those 73 patients for whom all three comparisons were available. In all of these patients a single eye was tested first. Most then had simultaneous bilateral testing. The results for the individual eyes in bilateral testing were put to double use, serving also as second test results in the repeated same eye, and opposite eye comparisons, respectively, for 68 of the 73 patients. The concordance

TABLE 3

ESTIMATED REPRODUCIBILITY OF TOPICAL TESTING IN THE GENERAL POPULATION

1st Test Category	Observed Concordance, %		Proportion of the General Population		Fractional Contribution, %
NN	71	×	0.58	=	41
NG	74	×	0.36	=	27
GG	79	×	0.06	=	5
			1.00		73

TABLE 4

TESTING OF OPPOSITE EYES ON DIFFERENT OCCASIONS

1st Test	2nd Test	All Tested	Initial IOP <20 mm Hg
NN	NN	18 (67%)	16 (67%)
NN	NG	9	8
NG	NN	3	1
NG	NG	44 (86%)	23 (92%)
NG	GG	4	1
GG	NG	4	0
GG	GG	4 (50%)	1 (100%)

TABLE 5

REPEAT TESTING OF THE SAME EYE ON DIFFERENT OCCASIONS

1st Test	2nd Test	All Tested	Initial IOP <20 mm Hg
pLpL	pLpL	44 (70%)	28 (78%)
pLpL	pLpH	18	8
pLpL	pHpH	1	0
pLpH	pLpL	23	17
pLpH	pLpH	22 (42%)	10 (32%)
pLpH	pHpH	8	4
pHpH	pLpL	2	0
pHpH	pLpH	11	5
pHpH	pHpH	21 (62%)	10 (67%)

TABLE 6

TESTING OF OPPOSITE EYES ON DIFFERENT OCCASIONS

1st Test	2nd Test	All Tested	Initial IOP <20 mm Hg
pLpL	pLpL	39 (71%)	25 (78%)
pLpL	pLpH	16	7
pLpH	pLpL	15	11
pLpH	pLpH	10 (36%)	5 (28%)
pLpH	pHpH	3	2
pHpH	pLpH	1	1
pHpH	pHpH	2 (67%)	0 (0%)

for simultaneous bilateral testing by final pressure criteria equaled or exceeded those seen for single eye and opposite eye testing in each category, but was not statistically significantly greater (Table 7). The concordances for simultaneous bilateral testing by change in pressure criteria exceeded those seen for single eye and opposite eye testing in each category, and the total of concordant responses was significantly higher for bilateral testing (Table 8).

Within this sample of 73 patients for whom all three tests were performed, the computed reproducibility of testing in the general population by final pressure criteria was 85% for bilateral, 80% for same eye, and 75% for opposite eye testing. By change in pressure criteria, the figures were 78% for bilateral, 57% for same eye, and 59% for opposite eye testing.

The correlation coefficients for regression analysis by final pressure criteria were .892 for bilateral, .729 for same eye, and .695 for opposite eye testing. By change in pressure criteria, the correlation coefficients were .850 for bilateral, .393 for same eye, and .372 for opposite eye testing.

The effect of the inclusion of spontaneous ocular hypertensives in the tested group—

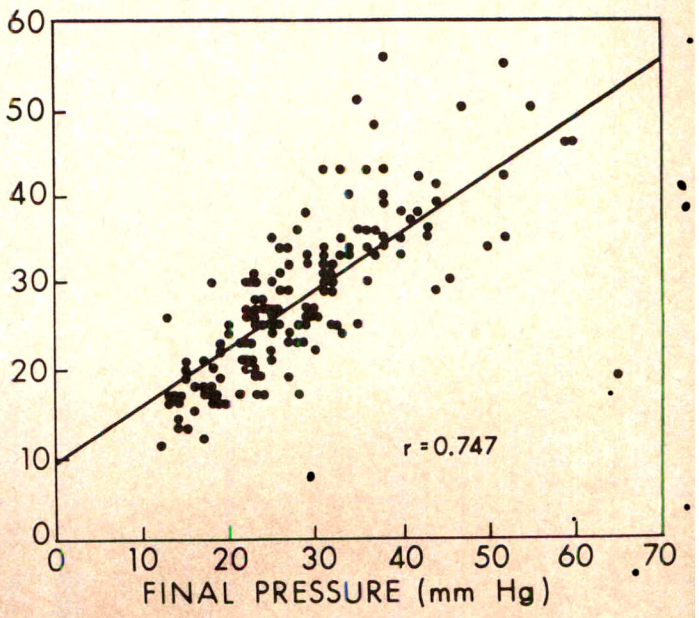


Fig. 1 (Palmberg and associates). Replicate ocular corticosteroid testing on the same eye on different occasions. Final pressure achieved on first test (abscissa) vs. that achieved upon second test (ordinate).

TABLE 7

COMPARISON OF SIMULTANEOUS BILATERAL, REPEAT SAME EYE, AND OPPOSITE EYE TESTING ON THE SAME PATIENTS

1st Test	2nd Test	Test		
		Simultaneous Bilateral	Repeat Same Eye	Opposite Eyes Separate Occasions
NN	NN	17 (81%)	19 (79%)	16 (70%)
NN	NG	4	5	7
NG	NN	0	2	1
NG	NG	44 (96%)	39 (85%)	42 (89%)
NG	GG	2	5	4
GG	NG	2	1	2
GG	GG	4 (67%)	2 (67%)	1 (33%)
Total concordant responses:		65 (89%)	60 (82%)	60 (82%)
Total discordant responses:		8	13	13

Among the 150 patients subjected to repeat same eye testing, 68 were spontaneous ocular hypertensives. Thus two of 31 NN responders, 32 of 70 NG responders, and 34 of 49 GG responders began the first test with an intraocular pressure of 20 mm Hg or more. None had an initial pressure in the GG range. To assess the effect of including ocular hypertensives in the tests, the results also were analyzed with the hyptertensives omitted (Table 1). There was slightly higher concordance in each category for the initially normotensive patients. The correlation coefficients for regression analysis of first and second test results were .747 for all patients, and .830 for those

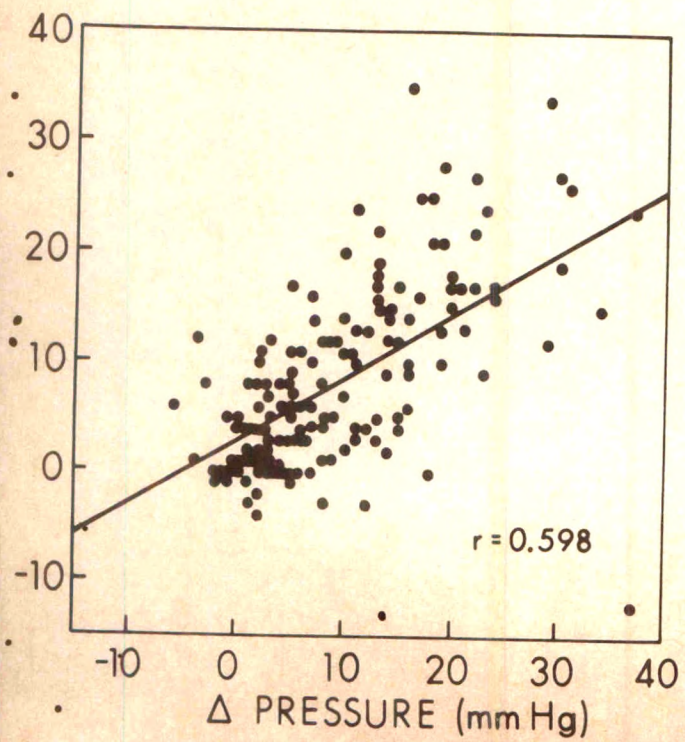


Fig. 2 (Palmberg and associates). Replicate ocular corticosteroid testing on the same eye on different occasions. Change in pressure on first test (abscissa) vs. that achieved upon second test (ordinate).

TABLE 8

COMPARISON OF SIMULTANEOUS BILATERAL, REPEAT SAME EYE, AND OPPOSITE EYE TESTING ON THE SAME PATIENT

1st Test	2nd Test	Test		
		Simultaneous Bilateral	Repeat Same Eye	Opposite Eye Separate Occasions
pLpL	pLpL	41 (87%)	35 (73%)	36 (75%)
pLpL	pLpH	6	12	12
pLpL	pHpH	0	1	0
pLpH	pLpL	8	14	13
pLpH	pLpH	13 (56%)	8 (33%)	8 (33%)
pLpH	pHpH	2	2	3
pHpH	pLpH	0	1	1
pHpH	pHpH	3 (100%)	0 (0%)	0 (0%)
Total concordant responses:		57 (78%)	43 (57%)	44 (60%)
Total discordant responses:		16	30	29

with initial pressure < 20 mm Hg. The effect of omitting ocular hypertensives was similar in the case of opposite eye testing (Table 4), and for same eye and opposite eye testing by the change in pressure criteria (Tables 5 and 6).

The effect of topical corticosteroid upon the intraocular pressure in the untreated contralateral eye—There were 94 patients who underwent two unilateral corticosteroid tests (either same eye or opposite eye), and who had no ocular disease in either eye. Upon first testing of these patients, we observed a rise in average pressure in the untreated contralateral eyes of pLpH and pHpH responders, and a fall in average pressure in the untreated contralateral eyes of pLpL responders. Upon second testing, however, we observed virtually no average change in pressure for any of the three categories (Table 9).

The pressure responses of the untreated contralateral eyes also were analyzed by the final pressure criteria (Table 10). The average fall in pressure in the untreated eye of NN responders on first testing was about half that noted for pLpL responders. It was reduced slightly on second testing. The

TABLE 9

EFFECT OF TOPICAL TESTING UPON INTRAOCULAR PRESSURE IN THE UNTREATED CONTRALATERAL EYE

First Test Category	No. of Persons	Net ΔP Untreated Eye	
		Test 1	Test 2
pLpL	28	−1.36 mm Hg ±2.98 (σ)	−0.14 mm Hg ±2.83
pLpH	35	+1.94 mm Hg ±4.24	+0.17 mm Hg ±4.32
pHpH	31	+1.58 mm Hg ±4.01	+0.19 mm Hg ±2.83

TABLE 10

EFFECT OF TOPICAL TESTING UPON INTRAOCULAR PRESSURE IN THE UNTREATED CONTRALATERAL EYE

First Test Category	No. of Persons	Net ΔP Untreated Eye	
		Test 1	Test 2
NN	15	−0.73 mm Hg ±2.96 (σ)	−0.53 mm Hg ±3.34
NG	32	−0.16 mm Hg ±4.19	+0.47 mm Hg ±2.87
GG	47	+2.02 mm Hg ±3.98	+0.02 mm Hg ±3.82

NG responders showed little average pressure change in the untreated eye on either test. The GG responders had a considerable rise in average contralateral pressure on the first test. This did not occur upon retesting (see Discussion).

Does the administration of topical corticosteroid to one eye affect the intraocular pressure response of the other eye during simultaneous testing?—Ninety-four persons had two uniocular (same or opposite eye) tests. In comparing the results of the tests, it was noted that NN patients achieved a higher mean pressure on the second test, by $+2.07 \pm 3.28$ mm Hg, a change which was statistically significant ($P < .05$ by paired t-test). The NG patients changed little, $+0.56 \pm 5.60$ mm Hg, but the GG patients reached a lower mean pressure on second test, by -3.53 ± 10.09 mm Hg, also a change which was significant ($P < .025$ by paired t-test).

This observation of significant differences between first and second test results for uniocular testing had to be taken into account in the subsequent assessment of bilateral testing. To find out if the administration of topical corticosteroid to one eye affected the intraocular pressure response of the other eye during simultaneous bilateral testing, we compared two sets of data, the first from persons tested unilaterally twice, and the second from persons tested uniocularly and then bilaterally. Specifically we compared the differences in mean final pressure by category for first and second uniocular tests (94 patients) to the corresponding differences found on uniocular and subsequent bilateral tests (68 other patients). The bilaterally tested patients gave virtually the same result as did the twice uniocularly tested patients in each of the three response categories (Table 11), demonstrating that application of corticosteroid to one eye in our sample has no discernable effect upon the intraocular pressure response of the other eye during simultaneous testing. Only two GG patients, however, were bilaterally tested.

Discussion

The results for replicate testing of the same eye show concordant responses for about three fourths (71% for NN, 74% for NG, and 79% for GG) of the patients in each response category (Table 1). When such data are used to estimate the reproducibility of topical testing in the general population, a value of 73% is obtained (Table 3). That value is but midway between chance (47%) and perfection (100%), yet is significantly different from chance ($P < .005$). Although the estimated general population reproducibility of 73%

TABLE 11

THE EFFECT OF TOPICAL CORTICOSTEROID UPON THE INTRAOCULAR PRESSURE RESPONSE OF THE OTHER EYE TO SIMULTANEOUS TESTING

First Test Category	Uniocular Test Followed by a Bilateral Test		Uniocular Test Followed by Another Uniocular Test	
	No. of Persons	Final P_2-Final P_1	No. of Persons	Final P_2-Final P_1
NN	23	+1.52 mm Hg ±4.36	15	+2.07 mm Hg ±3.28
NG	43	+0.63 mm Hg ±4.07	32	+0.56 mm Hg ±5.60
GG	2	−5.00 mm Hg ±7.07	47	−3.53 mm Hg ±10.09

also is greater than the 65% concordance found in the identical twin study, it is not statistically different.* It appears from our data that the poor concordance of identical twin results could be attributed to the limited reproducibility of topical testing. That being the case, topical testing is just not precise enough a pharmacogenetic indicator to test the validity of the monogenetic hypothesis.

Even though topical testing is a tool of limited precision when applied to whole populations, it remains a reasonably precise means of identifying high responders. Our data show, for example, that the reproducibility of a GG response is 79%, which compares favorably with a chance value of 6% (Table 2). By change in pressure criteria, the reproducibility of a pHpH response is 62%, compared to a chance value of 5% (Table 3).

Why doesn't topical testing yield more impressive results for the other categories? To attempt to answer that question let us first consider what factors may contribute to the apparent (observed) pressure response to topical corticosteroid. We may divide these into those factors affecting the "signal" of corticosteroid response and those contributing to the interfering "noise" of other influences on intraocular pressure. Factors affecting the signal probably include patient compliance in taking the drops on schedule for the full testing period, drug potency, period of retention of the drug in the tear film, corneal permeability of the drug, diffusion of the drug to its site of action, rate of removal of the drug from the eye, and the sensitivity of the drug receptors of the individual. Factors contributing to the noise may be subdivided into those associated with spontaneous differences in pressure between the eyes of an individual, those associated with spontaneous parallel variations in pressure, and those associated with pressure measurement itself (applanation tonometry).

Factors associated with spontaneous differences in pressure between the eyes of an individual probably include differences in blood supply to the ciliary body (seen in exaggerated form in unilateral carotid occlusion),[24] differences in neural supply that affect aqueous production,[25] and differences in the capacity of the outflow mechanism, which may be pathologically affected by angle anomaly, injury,[26] inflammation, or primary open-angle glaucoma. Factors associated with spontaneous parallel fluctuations in pressure may include endocrine, dietary, drug, and environmental influences upon diurnal variation,[27] and state of hydration.[28]

It should be possible experimentally to assess the relative contribution to replicate variance of the group of factors affecting signal, the group affecting spontaneous differences in pressure between opposite eyes, and the group affecting spontaneous parallel fluctuations. Data for such an assessment are available from the study of 73 patients that had replicate same eye, opposite eye, and bilateral tests (Tables 7 and 8).

Comparison of the reproducibility of replicate same eye and opposite eye tests should assess the variance which is due to the group of factors affecting spontaneous differences in pressure between opposite eyes plus any variance due to differences in actual responsiveness to corticosteroid. In Table 7 there is no difference in the number of concordant responses for same eye and opposite eye tests (60 concordant, 13 discordant), using final pressure criteria. Regression analysis by final pressure criteria yields correlation coefficients of .729 and .695, respectively. The slightly greater correlation for same eye testing is not significant (Fischer Z-transformation analysis).[29] No significant difference is found between replicate same eye and opposite eye testing when

* The comparison is made by chi-square analysis. The estimated general population sample (see Results) is composed of 39 concordant, and 14 discordant replicates. The twins have 24 concordant pairs, 13 discordant. $\chi^2 = 0.79$.

analyzed either qualitatively or quantitatively by change in pressure criteria. Thus factors affecting spontaneous differences in pressure between opposite eyes and differences between eyes in actual responsiveness to corticosteroid do not contribute appreciably to replicate variance in our sample.

Comparison of the reproducibility of replicate opposite eye and simultaneous bilateral tests should assess variance due to spontaneous parallel fluctuations in pressure, as during bilateral testing such changes occur in synchrony, and thus do not contribute to variance. In Table 7 we see greater concordance on bilateral testing (65 concordant, eight discordant) than on opposite eye testing (60 concordant, 13 discordant). While this difference in qualitative response is not statistically significant (by χ^2), the more sensitive quantitative analysis shows a highly significant difference ($P < .001$ by Fischer Z-transformation) between the correlation coefficients, which are .892 and .695, respectively. Even greater disparity is noted on analysis by change in pressure criteria, as would be expected since there are two opportunities for introduction of variance, once at the initial, and again at the ending pressure reading. Thus on bilateral testing 57 of the 73 responses are concordant as opposed to 44 on opposite eye tests ($P < .025$ by χ^2). The correlation coefficients, .850 and .372, are considerably different ($P < .001$). Thus factors associated with spontaneous parallel fluctuations in pressure (diurnal variation, state of hydration) appear to be responsible for a large part of the replicate error of topical testing. The remaining variance (represented by the difference between the estimated 85% reproducibility of bilateral testing and perfect concordance, or the difference between the correlation coefficient of .892 and perfect correlation) is attributable to factors affecting signal, and to the replication error of applanation tonometry.

Although this report may be the first to characterize the reproducibility of topical testing in a large number of patients, Becker[1,3] reported concordant responses for the separately tested opposite eyes of three patients, and Armaly[30,31] reported concordant responses for two of three patients. Levene and associates[9] reported that they performed bilateral testing in 56 patients suspected of having glaucoma. Their results were reported only as a plot of initial difference in pressure between eyes vs. final difference in pressure between eyes, so that it is not possible to deduce the actual concordance of responses. Kitazawa, Nose, and Saitoh[32] reported the results of bilaterally testing 128 persons, finding 95% concordance by change in pressure criteria. The difference between their results (122 concordant, six discordant) and ours (57 concordant, 16 discordant) is significant ($P < .005$ by χ^2). The difference does not seem attributable to our inclusion of ocular hypertensives, as when only those persons with initial pressure of < 20 mm Hg are considered, we still have only 29 of 37 concordant responses (78%).

We find that topical testing of one eye has no effect on the intraocular pressure of the untreated contralateral eye. Armaly[33] had reported that the pressure in the untreated contralateral eye of pLpH and pHpH responders rises significantly during testing, an average of $+1.6 \pm 0.6$ mm Hg ($P < .01$). Armaly attributed this rise to systemic absorption of dexamethasone. A fall in pressure of 0.9 ± 0.5 mm Hg in the untreated contralateral eyes of pLpL patients was noted as well. For his entire 80-patient sample the mean change in pressure in the untreated eye was -0.27 ± 2.64 mm Hg (computed from his Figure 1). Levene and co-workers[9] confirmed a contralateral rise in pLpH and pHpH patients ($+0.84 \pm 1.81$ mm Hg), and contralateral fall in pLpL patients (-0.67 ± 1.79 mm Hg). The mean change in pressure in the untreated contralateral eyes of all 96 of their patients was $+0.04$ mm Hg. The fact that there was no significant change in pressure for the whole

groups of patients tested by Armaly and Levene suggested to us that the observed changes in pressure in contralateral eyes were a reflection of the bias imposed upon the data by the classification system. Thus persons who would intrinsically be classified in the vicinity of the pLpL-pLpH border who happened to have a spontaneous fall in pressure in both eyes during testing, due to diurnal variation or change in state of hydration, would be observed to have a pressure response in the treated eye of ΔP intrinsic-ΔP spontaneous fall, and would be selected into the pLpL category. Those at the same border having a rise would be selected into the pLpH category. Similar effects would be noted at the pLpH-pHpH border. The untreated contralateral eyes of pLpL patients would then be enriched in eyes undergoing a spontaneous fall, and the mean contralateral pressure change would be negative. Similarly the pHpH category would be enriched in contralateral eyes that were undergoing a spontaneous rise in pressure. The pLpH category would be enriched more in those rising than in those falling as there would be more persons on the lower of the two borders of that group. This view can be tested.

Our suspicion is confirmed by the data in Table 9. We find, as did the previous investigators, that pLpL patients have a net fall in pressure in the untreated contralateral eye, and pLpH and pHpH have a rise, on first testing. But on second testing, when the bias of classification is removed by keeping persons in their first test category no matter what the result of the second test, we find that the changes in pressure in the untreated contralateral eyes virtually disappear. Similar results are found by final pressure criteria (Table 10).

We also find that topical testing of one eye has no effect whatever on the pressure response of the simultaneously tested other eye. The changes in final pressure responses between replicate tests are due to the bias of classification discussed above. Thus one needs to compare the results of persons tested uniocularly twice to those tested uniocularly and then bilaterally in order to show that testing of one eye has no effect on testing of the other eye (Table 11).

The importance of topical testing is that it demonstrates that increased in vivo sensitivity to corticosteroids is highly associated with primary open-angle glaucoma, and that it enables identification of nonglaucomatous persons in the general population who possess the same abnormal sensitivity who may then serve as subjects for prospective clinical studies.

The findings of topical testing have led to discovery of increased sensitivity to corticosteroids at the cellular level in glaucoma patients and GG responders by study of lymphocyte transformation inhibition[34,35] and leukocyte migration inhibition.[36] Persons with primary open-angle glaucoma also have increased systemic responsiveness to corticosteroids as demonstrated by dexamethasone suppression testing.[37] This multitude of evidence that patients with primary open-angle glaucoma have a body-wide increased sensitivity to corticosteroids, coupled with the knowledge that topical corticosteroid administration can mimic the disease in susceptible individuals, suggests a role for increased sensitivity to corticosteroid in the etiology of the disease.

Summary

The reproducibility of the intraocular pressure response to topical dexamethasone was investigated in 162 persons previously classified as low (NN), intermediate (NG), or high (GG) responders. The concordance of first and second test results was 71% for NN, 74% for NG, and 79% for GG responders, exceeding chance significantly for the NG and GG categories. Quantitative assessment revealed significant correlation of final pressure achieved on first and second tests ($r = .747$, $P < .001$).

In the course of the study applications of dexamethasone to one eye were noted to

have no effect on the intraocular pressure in the contralateral untreated eye, nor did testing of one eye influence the response of the contralateral eye in simultaneous bilateral testing.

Using our data to estimate the reproducibility of topical testing in a general population, a value of 73% was obtained. That value was similar to the 65% concordance reported in an identical twin study, suggesting that the limited precision of topical testing accounts for the relatively low concordance found in that study.

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Ophthalmic miniature

The difficulty with which we perceive the defect of the blind spot is well shown by the history of its discovery. Its existence was first demonstrated by theoretical arguments. While the long controversy whether the perception of light resided in the retina or the choroid was still undecided, Mariotte asked himself what perception there was where the choroid is deficient. He made experiments to ascertain this point, and in the course of them discovered the blind spot. Millions of men had used their eyes for ages, thousands had thought over the nature and cause of their functions, and, after all, it was only by a remarkable combination of circumstances that a simple phenomenon was noticed which would apparently have revealed itself to the slightest observation. Even now, anyone who tries for the first time to repeat the experiment which demonstrates the existence of the blind spot, finds it difficult to divert his attention from the fixed point of clear vision, without losing sight of it in the attempt. Indeed, it is only by long practice in optical experiments that even an experienced observer is able, as soon as he shuts one eye, to recognize the blank space in the field of vision which corresponds to the blind spot.

H. Helmholtz, The eye as an optical instrument.
In *Popular Lectures on Scientific Subjects*
London, Longmans, Green, and Co., 1873

THE HISTOPATHOLOGY OF PIGMENTARY DISPERSION SYNDROME WITH GLAUCOMA

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Although there have been several reports discussing the clinical aspects of pigmentary dispersion and its possible relationship to glaucoma,[1-8] there are few studies describing the histopathology of the pigmentary defect in the eyes.[9,10] We present the light and electron microscopic findings of the iris in a case of well-documented glaucoma with pigmentary dispersion. Additionally, an hypothesis as to the relationship of pigmentary dispersion and glaucoma will be discussed.

CASE REPORT

A 54-year-old white woman was referred to the clinical center with a diagnosis of pigmentary glaucoma and progression of field loss in the right eye despite maximum medical therapy. Family history was noncontributory for glaucoma. The patient had always enjoyed good health. Twelve years previously, bilateral elevated intraocular pressures with marked field loss in the left eye, and early field loss in the right eye, was diagnosed. On further examination, Krukenberg spindles, iris transillumination, and heavy pigment deposition on the trabecular meshwork was noted. Medical therapy was begun in 1959. Within the last two years, maximum therapy with pilocarpine and epinephrine topically and acetazolamide systemically failed to prevent progressive field loss.

When first seen in 1973, best corrected visual acuity was RE: 20/30 with a $-4.00 + 1.00 \times 30$; LE: counting fingers at 2 feet. There were bilateral heavy vertical Krukenberg spindles and marked midperipheral iris transillumination. Visual field demonstrated a concentrically constricted 10-degree field to all test objects in the right eye and a temporal island in the left eye. Gonioscopy indicated patchy areas of moderately heavy black pigment on sections of trabecular meshwork overlying Schlemm's canal, interspersed with areas of meshwork free of overlying pigment. There was pigment scattered over the surface of the iris and depigmentation of the ciliary body band bilaterally. On ophthalmoscopy, advanced optic nerve cupping was apparent. Diurnal curves on medical therapy demonstrated elevation of intraocular pressure from 18 to 32 mm Hg, usually reaching maximal levels in the early morning hours. True outflow facility measured while on treatment was RE: 0.09 µl/min/mm Hg, and LE: 0.03 µl/min/mm Hg. In view of the progression of field loss in a relatively young woman, trabeculectomy with peripheral iridectomy was performed in the right eye followed one week later by the same procedure in the left eye. The postoperative course has been uneventful.

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MATERIAL AND METHODS

The excised tissues from both operative procedures were fixed in 4% glutaraldehyde in 0.15M phosphate buffer (pH 7.2) for about 15 minutes at room temperature and then were cut into small pieces with appropriate orientation. The pieces were postfixed in 1% osmium tetroxide in the same buffer solution, dehydrated in ethyl alcohol, and were embedded in an epoxy resin. Sections 1 µ thick were stained with toluidine blue and were examined with the light microscope. Ultrathin sections were stained with uranyl acetate and lead acetate and were examined with the electron microscope.

RESULTS

Radial cross sections of the whole thickness of the iris from the right and left eyes were studied. The findings for both eyes were identical and only those for the right eye will be reported. Since the peripheral iridectomy was basal, the sphincter muscle zone was not included in the tissue studied, as demonstrated by a postoperative photograph of the right eye (Fig. 1). There appeared to be a slight increase in cellularity on the anterior surface of the iris and within the stroma and a few pigment-laden histocytes were found. Blood vessels and the surrounding tissue were normal.

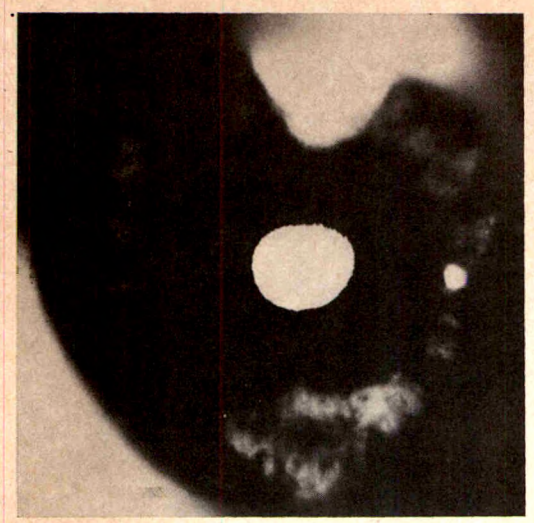


Fig. 1 (Kupfer, Kuwabara, and Kaiser-Kupfer). Site of iridectomy, postoperative, right eye. Noteworthy is the transmission of light in the mid-peripheral portion of the iris 360 degrees in circumference. The sphincter muscle zone is intact.

The most significant histologic findings were confined to the area of the mid-peripheral atrophic zone. Here, although the two-cell layer architecture was maintained, these two epithelial cell layers were thinned to about the thickness of a one-cell layer (Fig. 2). The outer epithelial cells were loosely packed with the formation of large lateral intercellular spaces (Fig. 3). The cytoplasm contained regular micro-organelles, but melanin granules were irregular in size and shape. Many melanin granules were fragmented. The basement membrane at the posterior surface was normal in thickness. An increased number of glycogen particles was noted in the cytoplasm. Of particular interest were the changes in the inner epithelial cells. The inner cells were atrophied and had lost their regularly fine basal processes of the dilator muscle (Fig. 4). Instead, the muscle portion of these inner epithelial cells appeared as large masses of separate muscle cells which showed well-differentiated components of smooth muscle, resembling in appearance the structure of the sphincter muscle (Figs. 5 and 6).

The smooth muscle cells were irregular in size and shape but contained well-differentiated muscle elements and a large amount of glycogen (Fig. 7). Although nerve fibers and their endings were found in the stroma, they were relatively sparse among the large masses of muscle cells. In addition, small degenerating cell elements in the muscle tissue appeared to be of neural origin. The surrounding connective tissue also contained a small amount of degenerating debris.

The trabeculectomy specimens from right and left eye verified the clinical impression

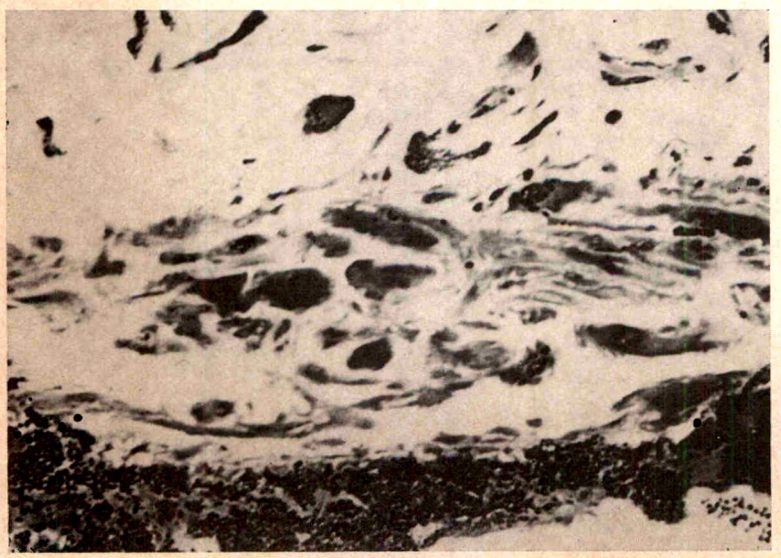


Fig. 2 (Kupfer, Kuwabara, and Kaiser-Kupfer). Iris showing areas of atrophy. The epithelial layer is thin and clusters of muscle cells are present in the stroma (toluidine blue, ×500).

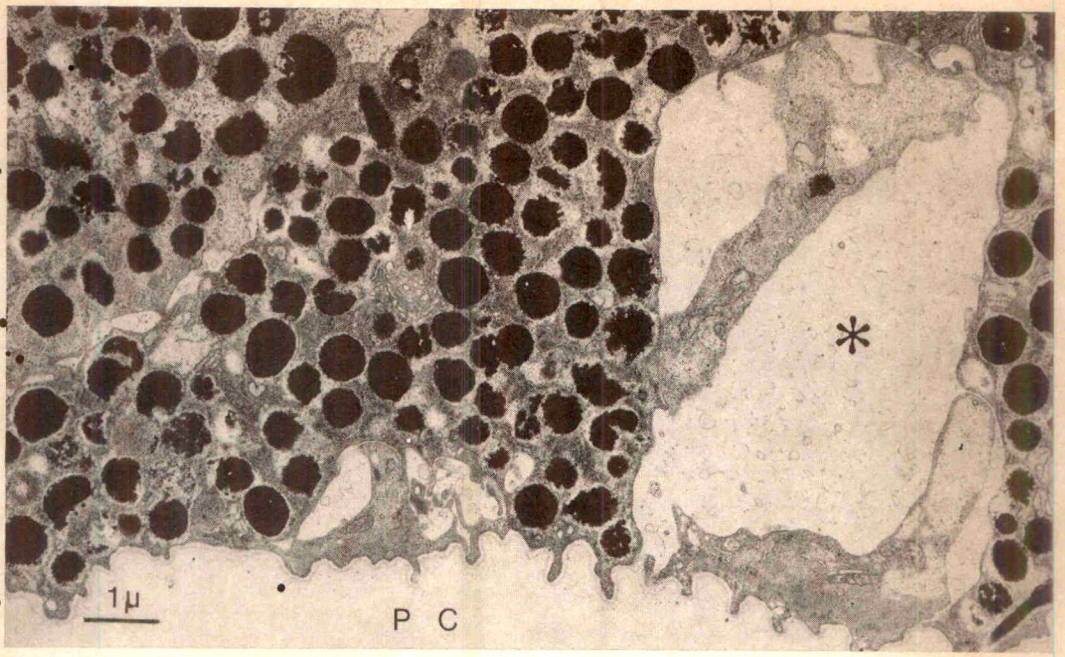


Fig. 3 (Kupfer, Kuwabara, and Kaiser-Kupfer). The outer epithelium in the area of iris atrophy. Large intercellular spaces are formed (asterisk). Melanin granules are fragmented. PC indicates posterior chamber (×10,000).



Fig. 4 (Kupfer, Kuwabara, and Kaiser-Kupfer). The epithelial layer in the area of iris atrophy. The inner epithelial cells are thin and their normal muscular portions are missing (arrow). Melanin granules are irregular in size and shape and many are fragmented. PC indicates posterior chamber (×10,000).

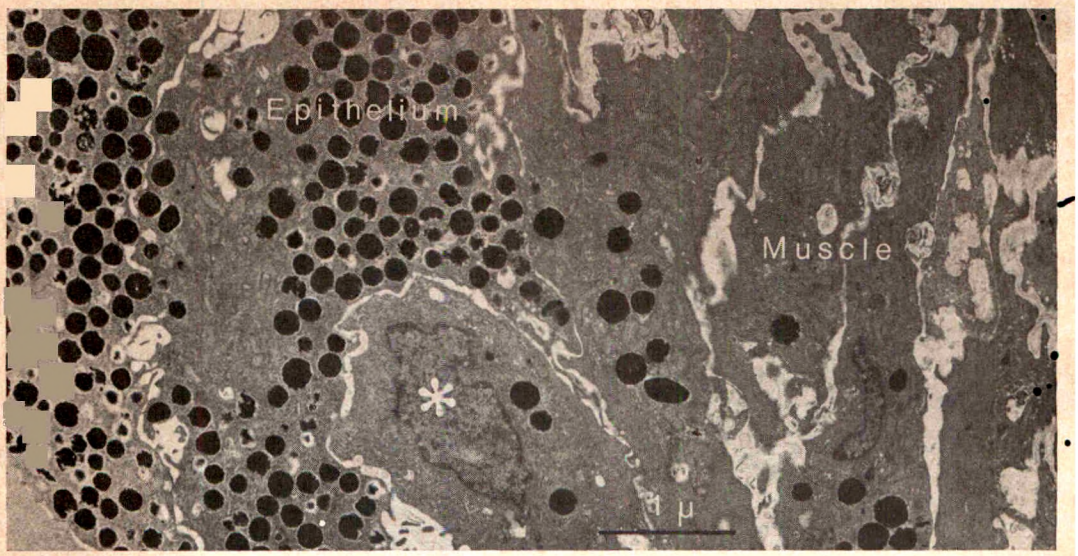


Fig. 5 (Kupfer, Kuwabara, and Kaiser-Kupfer). Proliferated muscle cells clustering in the area of iris atrophy. The pigmented epithelial cells have their bases at the posterior surface. The cell indicated with an asterisk appears to be one of the inner epithelial cells which are transforming into the muscle cells (×6,000).

of patchy areas of meshwork pigmentation. Although pigment was present, there was no increased amount seen. The remainder of the specimen appeared normal morphologically.

Discussion

Transillumination of the mid-periphery of the iris occurs in the pigmentary dispersion syndrome with or without glaucoma. It appears to be related in this case

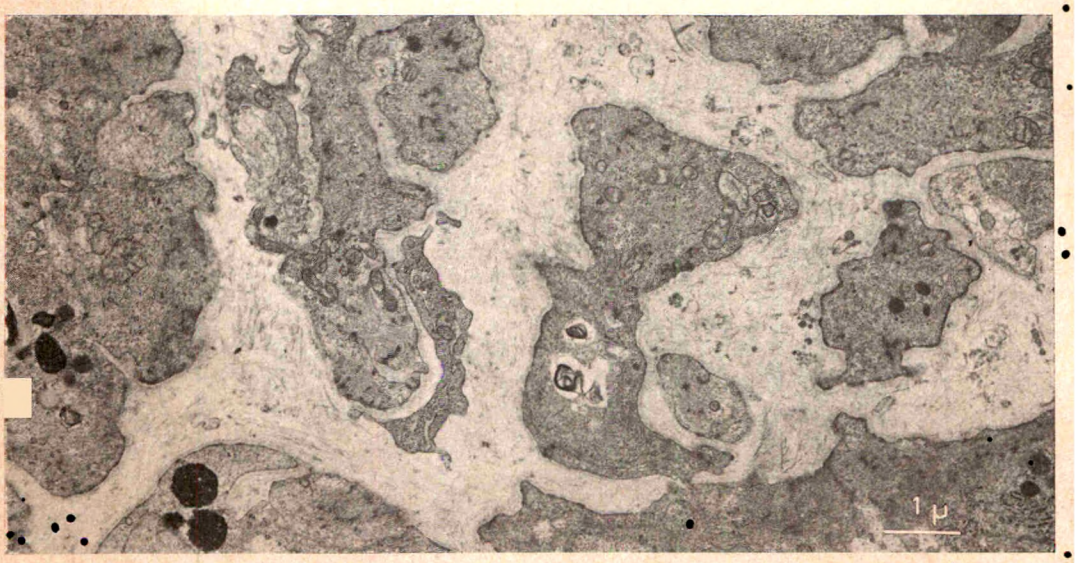


Fig. 6 (Kupfer, Kuwabara, and Kaiser-Kupfer). Clusters of muscle cells beneath the atrophied epithelium. Normal nerves are missing (×10,000).

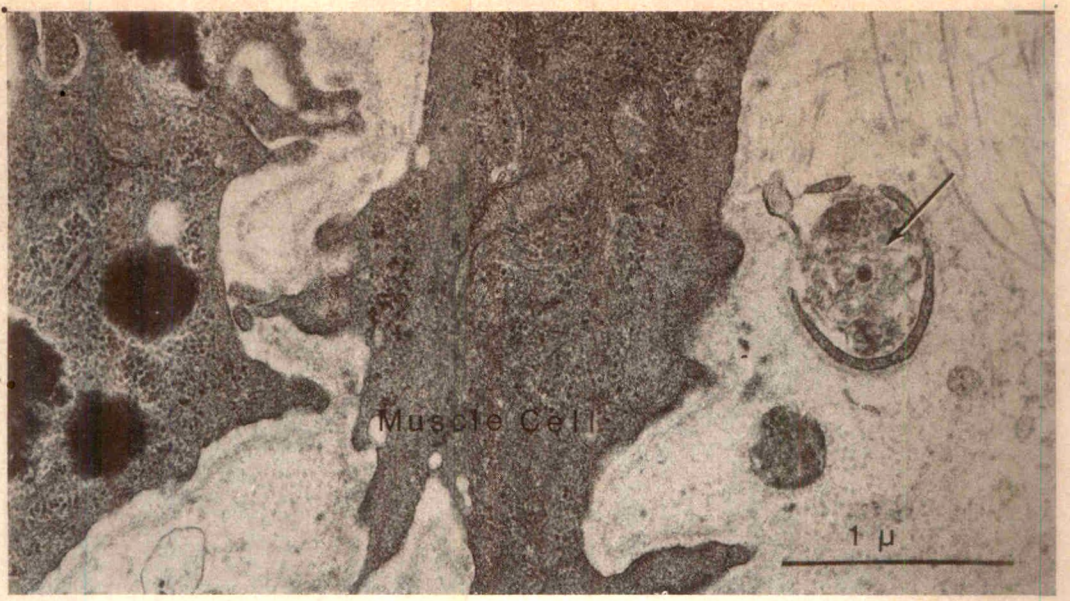


Fig. 7 (Kupfer, Kuwabara, and Kaiser-Kupfer). Higher magnification of the muscle cell. The cell shows the appearance of the normal smooth muscle. Some cell debris in the connective tissue appears to be degenerated nerve (arrow) (×30,000).

to the marked thinning of the epithelial cell layers in the iris as well as the formation of large intercellular spaces between the epithelial cells of the outer layer. The large intercellular spaces may also indicate the looseness of the outer epithelial cells with respect to the adherence of one cell to another as well as each cell to the inner layer. If such loose cells become knocked off with movement of the iris, adjacent cells may have to become thinner and cover the defect, leading to the thinning of the epithelial layers but with persistence of a two-layer arrangement. The pigmented epithelial cell that was knocked off the iris then became phagocytosed by either the corneal endothelial cells appearing clinically as a Krukenberg spindle, or by the trabecular meshwork endothelial cells overlying Schlemm's canal to form the pigment band, or by histiocytes on the anterior surface of the iris, or in the stroma, to produce the pigment dispersion of the iris surface.

The primary defect in this case, however, appears to be the poor differentiation of dilator muscle elements from the inner epithelial cells. The muscle fibers are not only separated from the epithelial cells, but are in great abundance and look like sphincter muscle. What could have caused these changes?

Firstly, this poor differentiation of the dilator muscle may represent a congenital or developmental anomaly, or both, occurring in those individuals who later demonstrate pigmentary dispersion syndrome with either Krukenberg spindle or pigment, or both, in trabecular meshwork but almost always with mid-iris transillumination. Whether glaucoma also is present may be coincidental. This possibility of pigmentary dispersion being a type of developmental abnormality was suggested first by Perkins and Jay.[6] There have been reports of Krukenberg spindle occurring in more than one member of a family,[2,7] and we are following a mother and daughter in one family as well as two brothers in another family who demonstrate evidence of pigmentary dispersion.

Secondly, the changes in the dilator muscle may be as a result of an interruption in the sympathetic nerve innervation. As noted previously, there was evidence of degenerating nerve elements found among the dilator muscle fibers in the atrophic iris region. Could these degenerating nerve elements lead to an increase in the number and size of the dilator muscle? It would be necessary to study dilator muscles in long-standing superior cervical ganglionectomy (in experimental animals) to answer this question.

Thirdly, it is possible that 13 years of treatment with pilocarpine and epinephrine may produce such changes. However, one would expect to see such characteristic lesions in other cases of open-angle glaucoma coming to pathology after many more years of treatment and this is not the case.

One is left with the tentative conclusion that the primary lesion in the pigmentary dispersion syndrome is an abnormality in both the inner and outer epithelial layers of the iris. In the outer layer, the epithelial cells appear loosely held to one another and fall off the iris, to be picked up by trabecular or corneal endothelial cells, thus leading to the characteristic trabecular pigmentation and Krukenberg spindle, respectively. In the inner layer, the epithelial cells appear to form dilator fibers of increased size and number, resembling sphincter muscle, associated with degenerated nerve elements. It would appear from these conclusions that the primary lesion in pigmentary dispersion is that of mid-iris transillumination (as demonstrated with a strong light applied to the sclera), which may be accompanied by Krukenberg spindle or trabecular pigmentation, or both. The occurrence of glaucoma in conjunction with this syndrome appears to be coincidental although the pigment in the trabecular meshwork may hasten the development of the elevation of the intraocular pressure. In any case, the glaucoma which may develop appears clinically as a simple open-angle glaucoma.

Summary

Iris tissue and trabecular meshwork, obtained at time of trabeculectomy, were studied using the light and electron microscope in a 54-year-old woman with pigmentary dispersion syndrome with glaucoma. The specific defect was a loss of the outer epithelial cells of the iris with marked thinning of the remaining outer layers so that the two-cell architecture of the iris epithelium was maintained. In addition, the radial muscle layer was increased in both number and size of muscle fiber. It would appear that the pigmentary dispersion syndrome may represent a congenital or developmental abnormality of the iris epithelium, or both, and that the glaucoma which occasionally occurs in conjunction with this syndrome is of the usual open-angle type.

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PRESSURE-INDUCED CHANGES IN THE ULTRASTRUCTURE OF THE ENDOTHELIUM LINING SCHLEMM'S CANAL

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Recently, we[1] showed by light microscopy and scanning electron microscopy in the living rhesus monkey that graded increases in intraocular pressure caused a commensurate increase in the number of vacuolar structures in the endothelium of Schlemm's canal. In this study, we describe the variations in the ultrastructure of this endothelium which occurred in response to graded alterations in pressures, and investigated the possibility that giant vacuoles may function as a pressure-dependent outflow pathway. In addition, we considered the pressure response of the other possible routes for the passage of aqueous humor through the endothelium (Table 1).

MATERIAL AND METHODS

We used 17 rhesus monkeys (body weight, 3 to 5 kg) in this study (Table 2). In each experiment, the animals were tranquilized with phencyclidine (1.5 mg/kg), anesthetized with thiopental sodium (Pentothal) (15 mg/kg), and killed with an overdose.

It was necessary to exclude the possibility that the artificial aqueous humor (Bárány's solution[18]), adopted as the perfusion fluid for the pressure experiments, had an adverse influence on the ultrastructure of the endothelium of Schlemm's canal. To do this the aqueous humor in the experimental eye of three animals was replaced with Bárány's solution via two 23-gauge intracameral needles connected to a continuous circuit of narrow-bore tubing filled with Bárány's solution. The perfusion fluid was passed into the anterior chamber by slow manipulation of a peristaltic pump and when replacement was complete the needles were left in situ for one hour. The control eye was then cannulated with two 23-gauge needles and both eyes were perfused before death with 2 to 4% phosphate-buffered glutaraldehyde by using the same continuous circuit technique.

The experimental procedure used for the pressure studies has already been described[1] and can be summarized as follows: We studied the effects of graded pressures in nine monkeys within the near physiologic range (8, 22, or 30 mm Hg) on the endothelium lining Schlemm's canal. The control eye of each animal was maintained at 15 mm Hg by means of an intracameral needle (25 gauge) attached to a reservoir containing Bárány's solution. The experimental eye was cannulated in a similar manner and attached to a second reservoir to maintain the intraocular pressure at either 8, 22, or 30 mm Hg (three eyes at each pressure level). After one hour, a second needle was introduced into each eye and was attached to a duplicate manometer system containing 2 to 4% phosphate-buffered glutaraldehyde. The reservoir containing mock aqueous humor was clamped and the fixative was allowed to infuse into the anterior chamber for 30 minutes, so the in vivo fixation took place at the same pressure as the corresponding artificial aqueous perfusion pressure.

In two animals, the control eyes were maintained at 15 mm Hg and the experimental eyes at 30 mm Hg in a manner similar to the previous experiment. However, the fixative was introduced via the common carotid arteries at a pressure slightly above normal arterial pressure (after division of the jugular veins) to determine whether or not the mode of fixative penetration had any influence on the morphologic findings.

This study was supported by grant 395, Scottish Hospital Endowment Research Trust, Edinburgh.

Reprint requests to I. Grierson, Tennent Institute of Ophthalmology, Western Infirmary and University of Glasgow, Glasgow, G11 6NT, Scotland.

TABLE 1

NONVACUOLAR ROUTES FOR THE PASSAGE OF AQUEOUS HUMOR THROUGH THE ENDOTHELIUM LINING THE TRABECULAR POSITIONS OF SCHLEMM'S CANAL*

	Routes	Mechanisms
Fine,[2,3] Feeney and Wissig,[4] Rohen and van der Zyphen,[5] Rohen,[6] van der Zyphen[7]	Intracellular	Micropinocytosis
Fine[2]		Pinocytosis involving marginal folds
Inomata, Bill, and Smelser,[8] Wulle[9]		Temporary intracellular channels (nonvacuolar)
Segawa,[10-12] Fink, Felix, and Fletcher[13]		Permanent intracellular channels (nonvacuolar)
Iwamoto[14]	Intercellular	Sondermann's canals
Vegge,[15] Rohen and van der Zyphen,[5] Rohen,[6] van der Zyphen[7]		Gaps between neighboring cells
Feeney and Wissig,[4] Shabo, Reese, and Gaasterland[16]		Intercellular clefts
Wulle[17]	Not specified	Gaps

* Proposed from transmission electron microscopy studies on the primate outflow apparatus.

Finally, in order to study the effects of pressures outside the physiologic range on the endothelium, intraocular pressures in both eyes of three animals were maintained for one hour at 0 and 50 mm Hg, respectively. The eyes maintained at 50 mm Hg were fixed in vivo by anterior chamber infusion and the eyes at 0 mm Hg by immersion after in vivo enucleation; in the latter eyes, the anterior segments were excised immediately after immersion and the lenses were removed.

The eyes fixed by intracarotid and intracameral in vivo perfusion were left in situ for ten to 30 minutes after the termination of fixative infusion. The anterior segments were excised and immersed in the primary fixative solution. The anterior segments were divided into quadrants 30 minutes later and the tissue was kept in phosphate-buffered glutaraldehyde for at least 24 hours. Meridional blocks of limbal tissue were cut from each quadrant and after secondary fixation in 1% osmium tetroxide, the tissue blocks were dehydrated in graded alcohols, cleared in propylene oxide, and embedded in Araldite. Sections (60 to 80 nm thick) were cut in the meridional plane on an LKB ultramicrotome III and viewed after uranyl acetate and lead citrate staining, by using either the Siemens 1A or the Phillips 300 electron microscopes. The morphologic as-

TABLE 2

EXPERIMENTS PERFORMED AND MODES OF PRIMARY FIXATIVE PENETRATION

Experiment	No. of Animals	Intraocular Pressure (mm Hg)		Mode of Fixation
		Experimental Eye	Control Eye	
To assess the suitability of Bárány's solution	3	Not regulated		Anterior chamber infusion
To investigate the effects of pressure within the near physiologic range	3	30	15	Anterior chamber infusion
	3	22	15	Anterior chamber infusion
	3	8	15	Anterior chamber infusion
To assess the mode of fixative penetration	2	30	15	Carotid perfusion
To investigate the effects of pressure outside the physiologic range	3	50	—	Anterior chamber infusion
		—	0	Immersion

sessment of the endothelium was based on tissue mapping of single, thin sections and extensive serial reconstruction.

Results

The tissue exposed to Bárány's solution for one hour failed to demonstrate any significant difference between the ultrastructure of this tissue and that of the corresponding controls. Similarly, comparison of the ultrastructure of the outflow apparatus after two methods of fixation (that is, intracameral infusion and common carotid perfusion) did not reveal any significant morphologic differences at the two pressures investigated (15 and 30 mm Hg).

The near physiologic range—Intraocular pressure, 15 mm Hg (Control tissue)—The endothelial cells lining the trabecular wall of Schlemm's canal were generally squat and had a patchy and irregular basement membrane. The ultrastructural features of the cells at this pressure were similar to those described in the normal primate outflow system by previous authors,[2,4,8,15,19–24] and briefly were as follows: The perinuclear region of the cells was prominent and bulged into the canal lumen. Small mitochondria with dense matrices, cisternae of rough endoplasmic reticulum, and stacks of the Golgi apparatus were found most frequently in the perinuclear cytoplasm, but were not abundant in the endothelial cells. Primary lysosomes, multivesicular bodies, smooth endoplasmic reticulum, glycogen, and lattice-like crystals were also identified in the cells. Small vesicles (approximately 30 nm in diameter) with a distinctive electron-dense spiny coat were dispersed throughout the cell cyto-

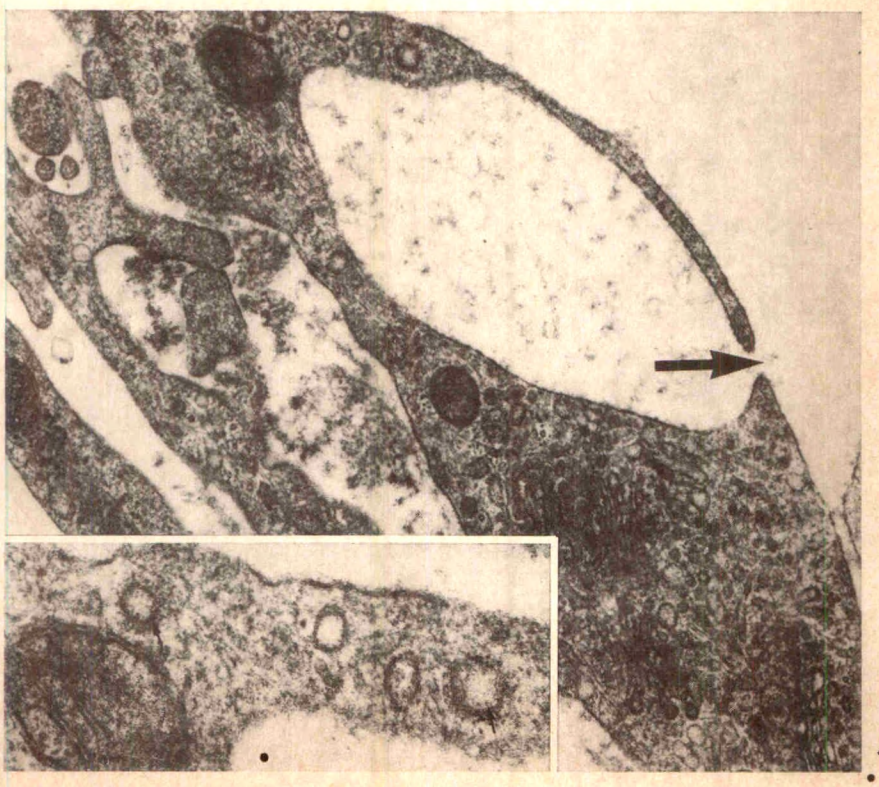


Fig. 1 (Grierson and Lee). At 15 mm Hg, there is a giant vacuole with a canal opening (arrow). These pores were usually small and rare at this pressure (×33,000). Inset, Coated micropinosomes (small arrows) are seen in part of the endothelial cell cytoplasm (×72,000).

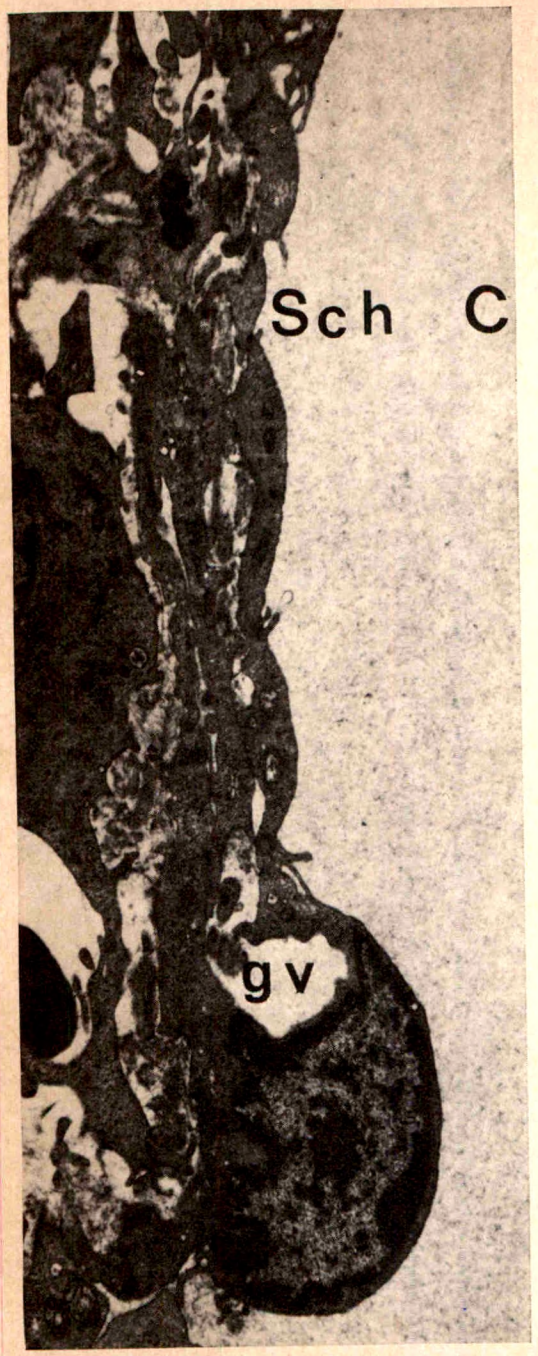


Fig. 2 (Grierson and Lee). At 15 mm Hg, the cells of the trabecular endothelium are squat and form a continuous monolayer. Giant vacuoles (gv) are identified occasionally, particularly in the prominent perinuclear regions that bulge into the lumen of Schlemm's canal (Sch C) (×6,400).

plasm, were often prevalent around the Golgi apparatus, and were present within the lumen of multivesicular bodies. To our knowledge, the structures have not been previously described in detail in these endothelial cells but have been noted in retinal pigment epithelium.[25] We paid particular attention to the identification of structures in the endothelium that have been considered as possible routes for the passage of aqueous humor into Schlemm's canal.

Micropinocytosis—The small vesicles (or micropinosomes), generally thought to be involved in the active intake of fluid, were found most frequently at or only a few nanometers from the luminal surface of the endothelial cells and were fewer at the meshwork surface. Two distinct types of micropinocytotic vesicles were observed, an uncoated vesicle (60 to 80 nm in diameter) bounded by a smooth membrane and, seen only rarely, a coated vesicle (approximately 100 nm in diameter) which had electron-dense material on both surfaces of its limiting membrane (Fig. 1).

Pinocytosis—Larger vesicles, which appeared to be formed by the folding over of cytoplasmic projections from the cell surface (Figs. 2 and 3), were usually adjacent to the zone of apposition between neighboring endothelial cells; similar cytoplasmic projections were described by Fawcett[26] in capillary endothelia and were called marginal folds.

The term pinocytosis has been used to describe a variety of processes by which cells imbibe fluid but in this text the term is confined to the process of large vesicle formation from projections of cell processes (to distinguish it from the process of micropinocytosis). Pinocytotic vesicles were not particularly prevalent at 15 mm Hg.

Intercellular and intracellular gaps—Gaps, up to 3 μ wide, were identified occasionally in the endothelium and these openings were sometimes occupied by a nonendothelial cell that we presumed was in transit. In single thin sections it was not possible to determine

whether or not the gaps were inter- or intracellular channels. However, on all occasions when successful serial sectioning was possible, the gaps were intracellular (Fig. 4). Invariably the channels were found in the narrow marginal regions of the endothelial cells.

Sondermann's canals—Invaginations of the endothelium lining the trabecular wall often penetrated into the meshwork. Although these will be referred to as Sondermann's canals, they were not shown to communicate with intertrabecular spaces.

Minipores—Small fenestrations or minipores, about 0.1 μ wide and bridged by a diaphragm, were occasionally observed in segments of attenuated endothelial cell cytoplasm, for example, at the periphery of the cells or in the walls of the larger vacuoles (Fig. 5).

Giant vacuoles—Giant vacuoles were observed in the endothelium lining the trabecular wall at 15 mm Hg pressure, but were not a prominent feature and were rare in the endothelium lining the bridging septae. The vacuoles were of variable size (between 1 and 8 μ in diameter), were lined by a smooth single limiting membrane, and were surrounded by the cytoplasm of a single endothelial cell. Cytoplasmic microfilaments were in close association with the vacuolar membrane and appeared to be more concentrated in the cytoplasm at the apex and the base. Although, from the study of single thin sections, many of the giant vacuoles appeared to be intracytoplasmic, all the successful serial reconstructions of the endothelial cells containing giant vacuoles revealed a pore (approximately 1 μ wide) in the meshwork position of the cell. The

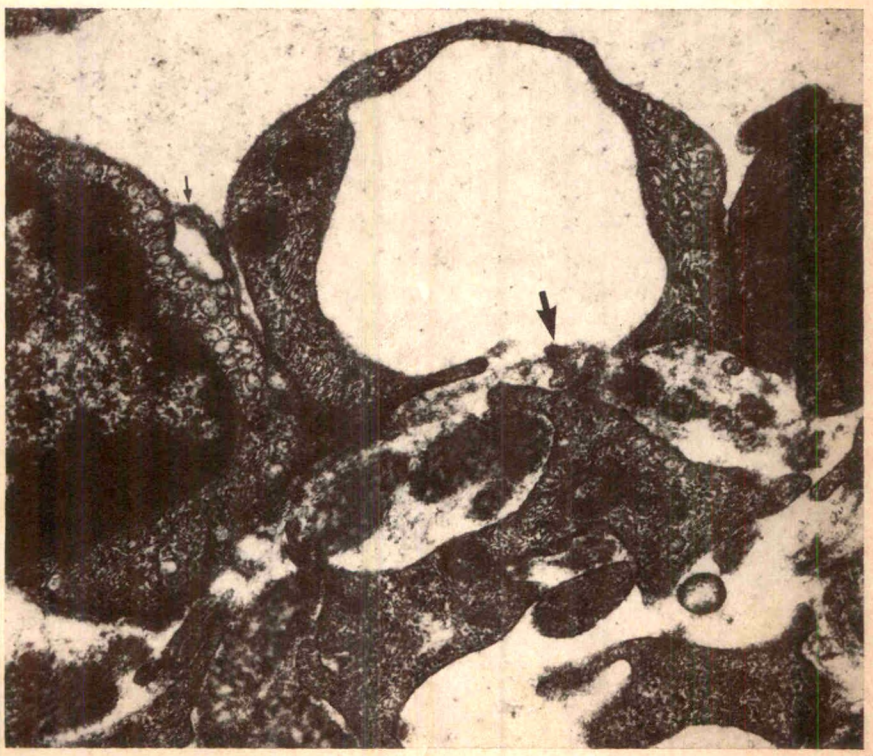


Fig. 3 (Grierson and Lee). At 15 mm Hg, there is a giant vacuole with an opening on the meshwork position (large arrow). Ground substance and cellular processes from the endothelial meshwork are in close association with the pore. Smooth-coated micropinocytotic vesicles are evident in the endothelial cells and a larger pinocytotic vesicle is indicated by a small arrow (×25,000).

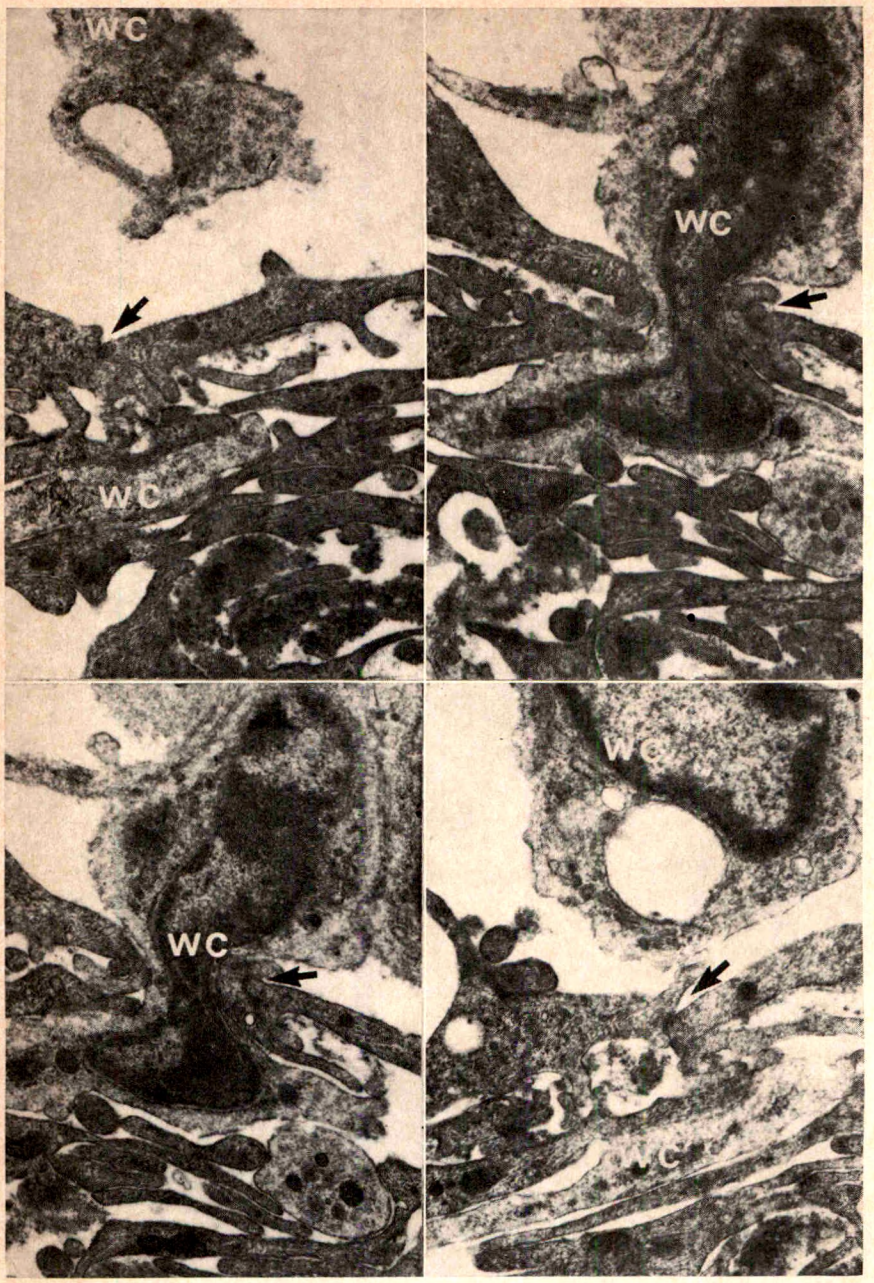


Fig. 4 (Grierson and Lee). At 15 mm Hg, there are four serial sections of a wandering cell (WC) within the endothelium. An arrow indicates the region of apposition between the two endothelial cells in the lining layer. The wandering cell occupies a nonvacuolar channel within the left endothelial cell (×17,000).

pores which were short in the vertical axis (less than 0.3 μ) were lined by a smooth membrane in continuity with that of the vacuole and the plasma membrane of the endothelial cell. Ground substance and cell processes from the underlying endothelial meshwork cells were in close association with the meshwork pore (Fig. 3). Vacuolar pores opening into the canal lumen, or lumen pores, were identified infrequently at

15 mm Hg, and were usually smaller than the pores on the meshwork position (Fig. 1).

The cells lining the corneoscleral wall of the canal were more attenuated than those on the trabecular wall and had a distinctive and continuous basement membrane. The perinuclear bulge was less prominent and giant vacuoles, minipores, and lattice-like crystals were not identified.

INTRAOCULAR PRESSURE, 8 MM HG—At 8 mm Hg, the canal lumen contained red cells and "flocculent" material thought to be coagulated plasma protein. Sondermann's canals, intracytoplasmic gaps, and minipores were not identified in the endothelium. There were many micropinocytotic vesicles (both smooth and coated) in evidence, particularly on the luminal surface, and pinocytotic folds were prominent at the cell margins (Figs. 6 and 7).

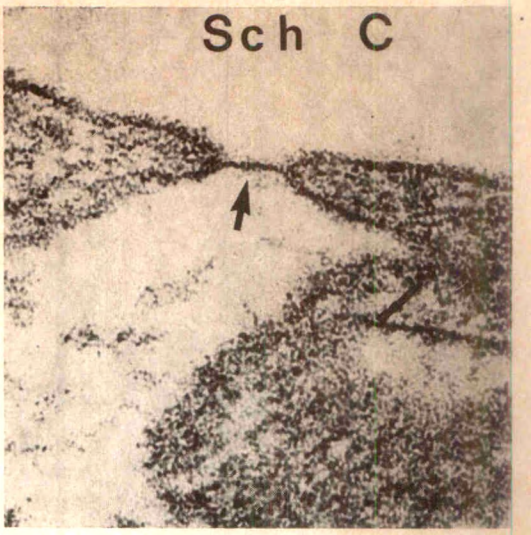


Fig. 5 (Grierson and Lee). At 15 mm Hg, a small diaphragmed pore (minipore) is indicated by an arrow. These minipores are found in regions where the endothelium is attenuated; Schlemm's canal, Sch C (×155,000).

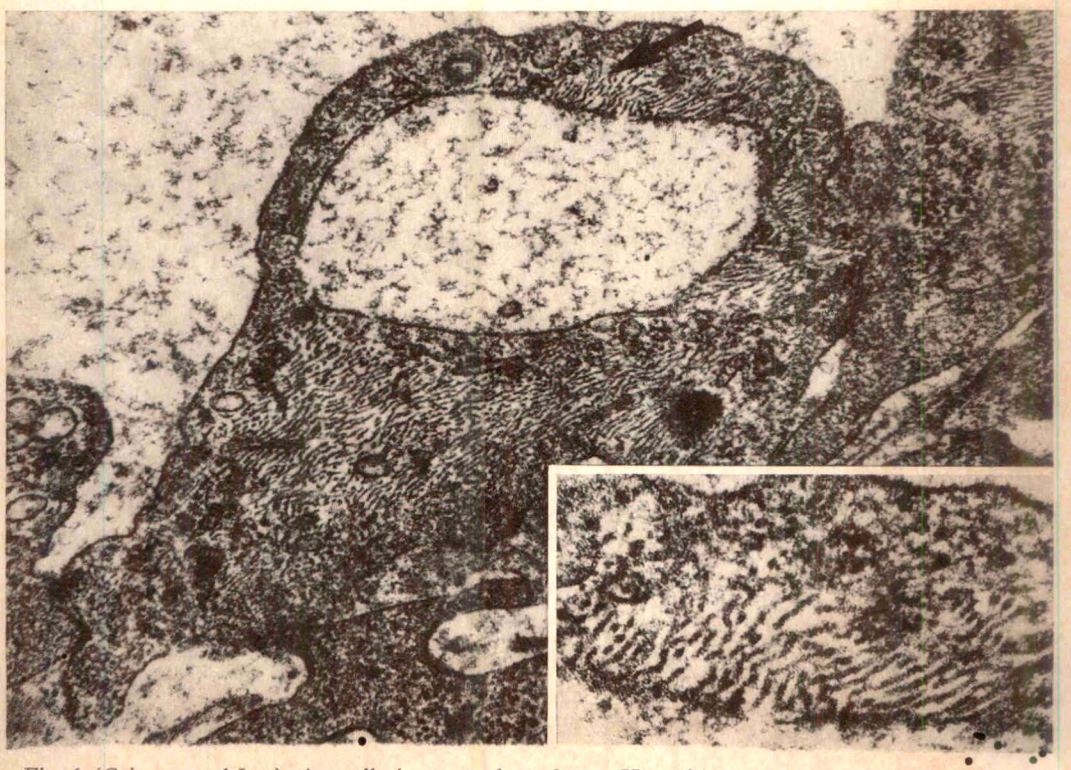


Fig. 6 (Grierson and Lee). A small giant vacuole at 8 mm Hg. Although no openings are evident, the concentration of flocculent material within the vacuole is similar to that in the canal lumen. The region shown in the inset is indicated by an arrow. The microfilaments of the cell cytoplasm are inserted into the membrane of the giant vacuole (×38,000; inset, ×106,000).

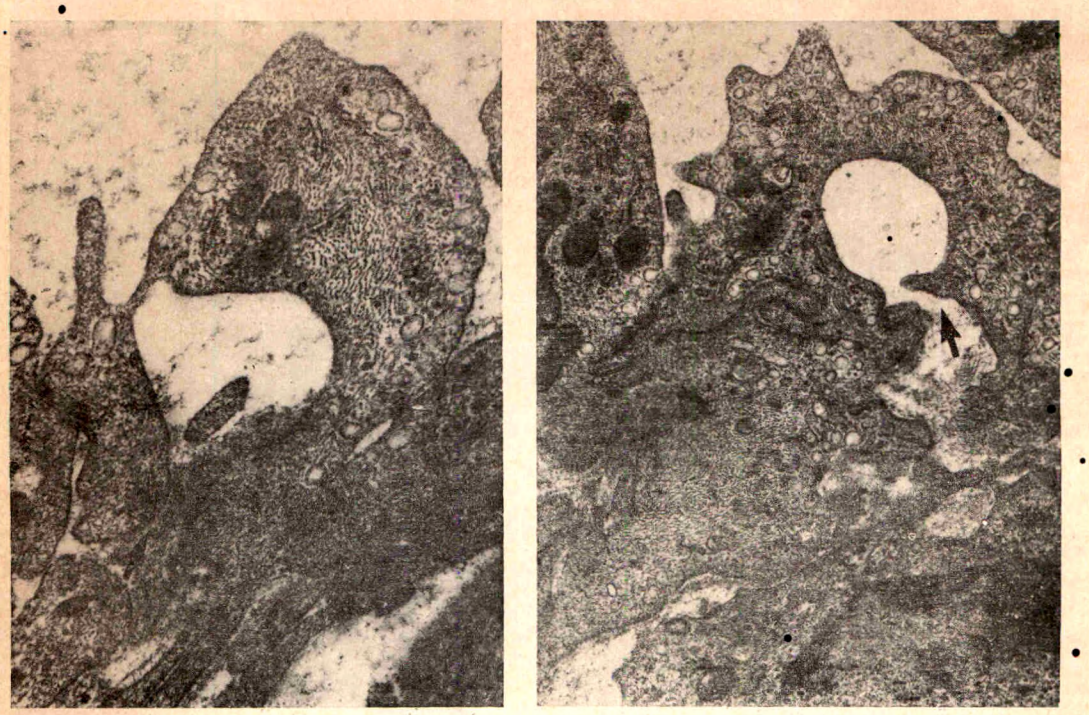


Fig. 7 (Grierson and Lee). The giant vacuoles have openings on the meshwork position (arrows). At 8 mm Hg the channels are long, narrow, and tortuous and often the passageway is blocked with ground substance. Many micropinocytotic vesicles are found within the endothelial cell cytoplasm (left, ×30,000; right, ×19,000).

Giant vacuoles were rare and were small (less than 4 μ in diameter) in the endothelium lining the trabecular wall and were not found in the endothelium lining the bridging septae. The vacuoles were always delineated by a single membrane and fortuitous sections demonstrated intimate association between this membrane and the closely packed cytoplasmic microfilaments. The vacuolar lumen sometimes contained flocculent material of similar density to that observed in the canal (Fig. 6). Lumen pores were not identified but we identified meshwork pores, which were longer in the vertical axis (up to 2 μ) and more cylindrical (less than 1 μ in diameter) than those observed at 15 mm Hg. Ground substances from the underlying meshwork were in close association with these passageways and often appeared to fill the lumen of the pore (Fig. 7).

INTRAOCULAR PRESSURE, 22 MM HG—The presence of numerous giant vacuoles in the undulating endothelium at this pressure provided the opportunity to study a larger population of these structures by serial reconstruction. Three types of giant vacuoles were identified in this tissue: (1) vacuoles with one or more meshwork pores, but without a lumen pore—this type of vacuole was the most common; (2) vacuoles with both meshwork and lumen pores (0.2 to 1.4 μ) so that a transcellular channel was formed (Figs. 8 and 9); and (3) vacuoles (usually small and less than 2 μ wide) with a lumen pore but without a meshwork pore (Fig. 10).

Minipores and intracellular nonvacuolar channels were identified in the marginal cytoplasm of the endothelial cells.

INTRAOCULAR PRESSURE, 30 MM HG—Many giant vacuoles of variable size were in the endothelium lining the trabecular aspect of Schlemm's canal and the largest

vacuoles (up to 15 μ wide) were surrounded by attenuated cytoplasm (Fig. 11). Many endothelial cells contained more than one vacuole. However, serial reconstruction showed that the vacuoles were frequently in communication and could be considered to be one large multiocular structure (Fig. 12). In addition to their presence in the endothelium lining the trabecular aspect of the canal there were many vacuoles in the endothelium lining the septae and an occasional vacuole was observed in the endothelium lining the corneoscleral aspect of the canal. The three types of giant vacuoles described in the endothelium at 22 mm Hg were identified at 30 mm Hg. Giant vacuoles with meshwork pores were the most abundant and although vacuolar transcellular channels and vacuoles with a lumen pore constituted only some of the vacuole population, they were found more frequently than at the lower pressure because of the overall increase in vacuole numbers.

The meshwork pores were broad (up to 6 μ in diameter in the largest vacuoles) and short in the vertical plane and frequently more than one meshwork pore was found in the larger giant vacuoles. The meshwork pores were usually free from extracellular material and the endothelial meshwork cell processes that were in close association with the pores of many giant vacuoles at lower pressures (Fig. 13). The less frequently observed lumen pores were smaller than the

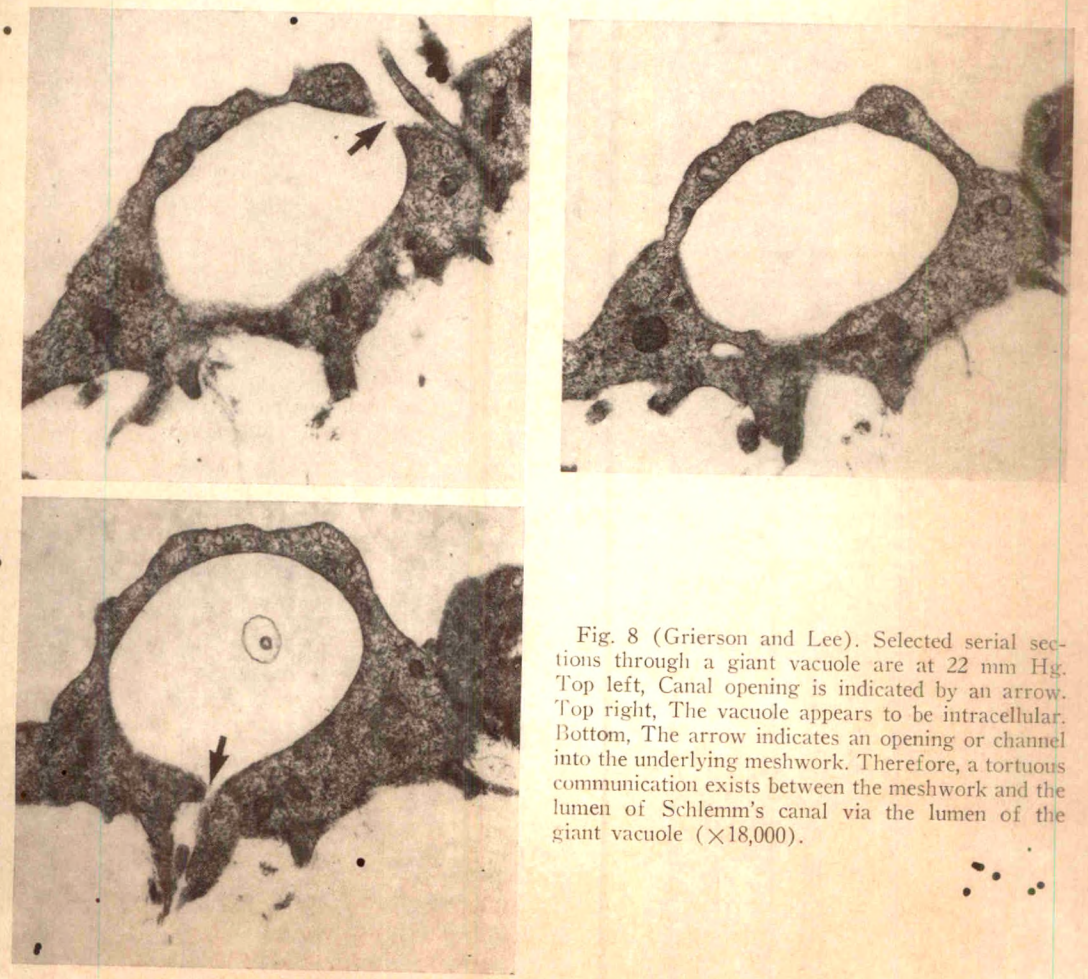


Fig. 8 (Grierson and Lee). Selected serial sections through a giant vacuole are at 22 mm Hg. Top left, Canal opening is indicated by an arrow. Top right, The vacuole appears to be intracellular. Bottom, The arrow indicates an opening or channel into the underlying meshwork. Therefore, a tortuous communication exists between the meshwork and the lumen of Schlemm's canal via the lumen of the giant vacuole (×18,000).

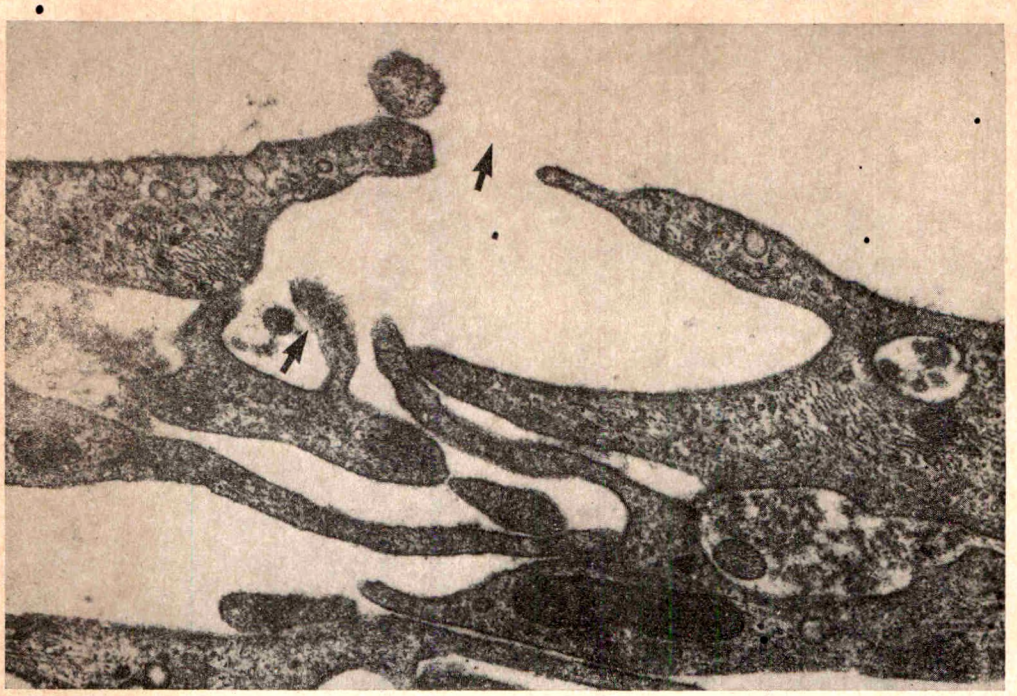


Fig. 9 (Grierson and Lee). At 22 mm Hg both pores in this giant vacuole have been included in the same plane of section. Microfilaments are in close association with both the membrane of the vacuole and the meshwork pore (×21,000).

meshwork pores (they varied in diameter from 0.2 to 2.5 μ) and two pores were rarely seen in the one vacuole.

Gaps in the endothelium lining the trabecular aspect of Schlemm's canal were more evident than at lower pressures. The increase was due partly to intracellular channels (Fig. 14), only found in the narrow marginal regions of the cells, and partly to cellular separation although the latter was relatively uncommon. Fenestrated minipores were found frequently in attenuated regions of the endothelium and as this lining layer was highly convoluted, deep invaginations (or Sondermann's canals) were abundant. There were fewer micropinosomes (both smooth and coated forms), particularly on the apical surface of the endothelium where they had been prevalent at lower pressures; pinocytotic vesicles were similarly reduced in numbers. The decrease in pinocytosis and micropinocytosis was observed not only on the endothelium lining the trabecular aspect of the canal but also in the endothelium lining the septae and the corneoscleral aspect of the canal. There were no other changes in organelle content from that seen in the control endothelium at 15 mm Hg (for example, the number of mitochondria and the amount of rough endoplasmic reticulum remained constant) apart from a slight increase in the numbers of lysosomes and lysosomal complexes.

Nonphysiologic pressure—INTRAOCULAR PRESSURE, 0 MM HG—Giant vacuoles, nonvacuolar channels, minipores, and Sondermann's canals were not found in the endothelium lining the trabecular aspect of the canal. There were occasional bulges formed by the cell nuclei that protruded into a canal lumen which contained red cells and flocculent material (Fig. 15).

In the endothelium lining the canal (including that on the corneoscleral aspect), smooth and coated micropinocytotic vesicles were abundant, particularly under the apical surfaces of the cells. The coated vesicles were larger (up to 150 nm in diameter)

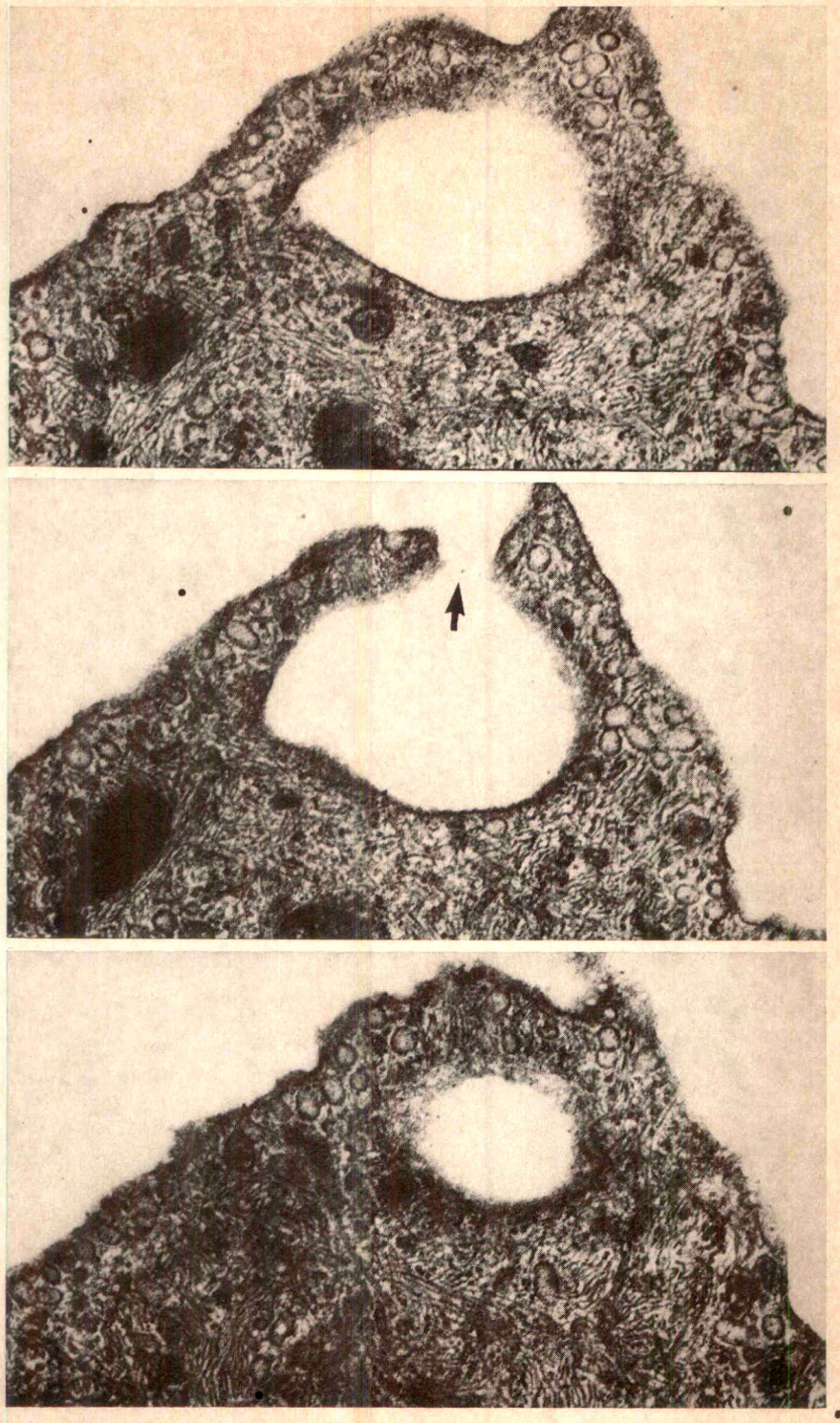


Fig. 10 (Grierson and Lee). Selected serial sections through a giant vacuole are at 22 mm Hg. This structure has an opening into the canal lumen (arrow) but no opening into the meshwork. It is, therefore, a deep flask-like invagination from the canal aspect of the endothelial cell (×48,000).

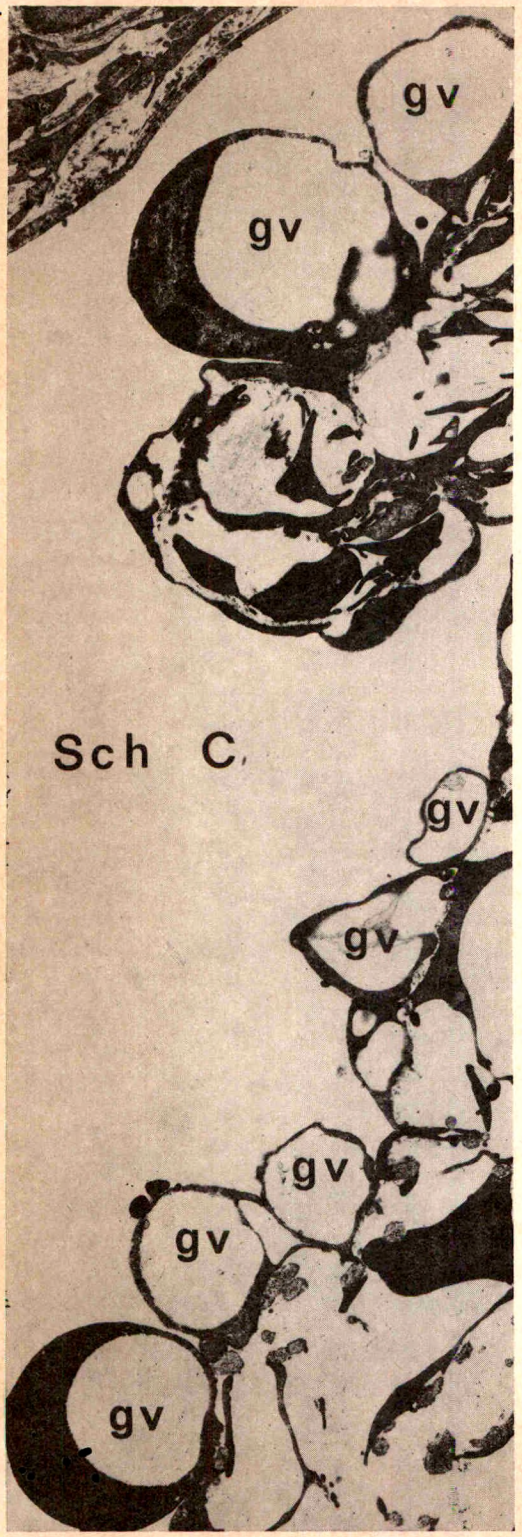


Fig. 11 (Grierson and Lee). Part of the trabecular wall lining Schlemm's canal (Sch C) at 30 mm Hg holds many giant vacuoles (gv). Some of the vacuoles are large and indent nuclei (×3,800).

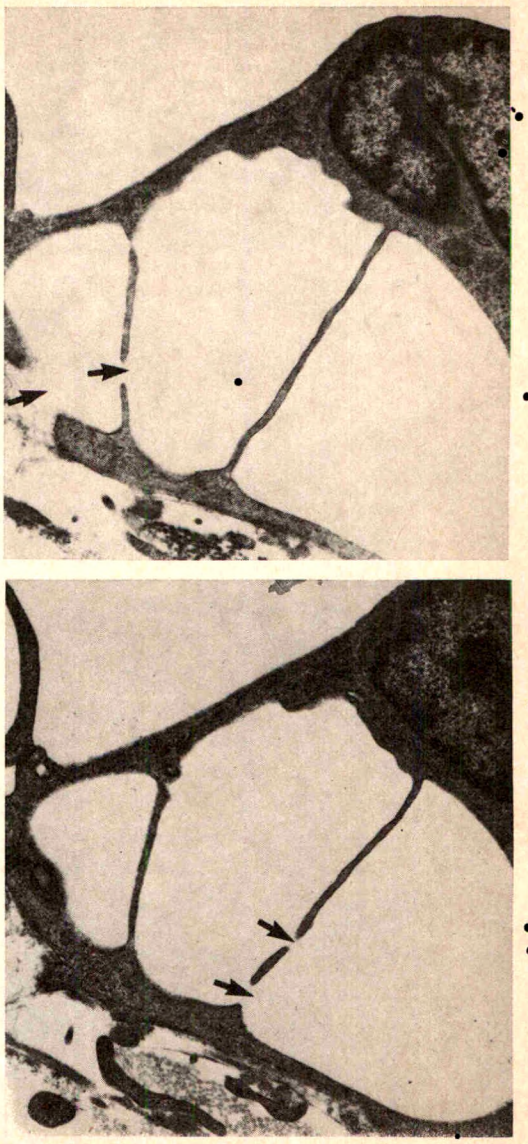


Fig. 12 (Grierson and Lee). Serial sections of a multilocular giant vacuole at 30 mm Hg. A meshwork pore and openings are seen between the lobes of the giant vacuole. Therefore, this is considered as one vacuole with intercommunicating chambers rather than separate vacuoles (×12,000).



Fig. 13 (Grierson and Lee). A giant vacuole at 30 mm Hg and the meshwork opening (arrow). Unlike the meshwork openings at lower pressures, little ground substance obstructs the opening (×20,000).

and of more complex ultrastructure than those previously described. The vesicle membrane had a thicker inner (luminal) coat and the outer (cytoplasmic) coat, in addition to being thicker and more intensely staining, had striations or spokes that gave the vesicles a spiny appearance (Fig. 16). Uranyl acetate en bloc* staining emphasized not only the distinct nature of the cytoplasmic and luminal coats (showing each to be adherent to separate lipid leaflets of the trilaminar limiting membrane) but also the similarity between the electron-dense material in the lumen of the vesicle and that in Schlemm's canal (Fig. 17). The larger pinocytotic vesicles were also present; not only were they formed from marginal folds but also by small processes that projected from the luminal surface in the perinuclear region of the cell (Fig. 18). Lyosomes were prominent in many of the endothelial cells.

INTRAOCULAR PRESSURE, 50 MM HG—Much of the canal lumen was occluded and giant vacuoles were concentrated in the posterior region where the canal was patent. The vacuoles were often large and had large meshwork pores and frequent openings into the canal lumen. Often several canal openings were present in the one vacuole (Fig. 19) but they usually appeared to be ragged deficits, which were not membrane lined, rather than true pores. Similarly, there were often deficits between neighboring cells in the endothelium. In the anterior region where the trabecular wall endothelium was

* Some tissue blocks were treated with uranyl acetate before dehydration (to emphasize the cell membranes).[27]

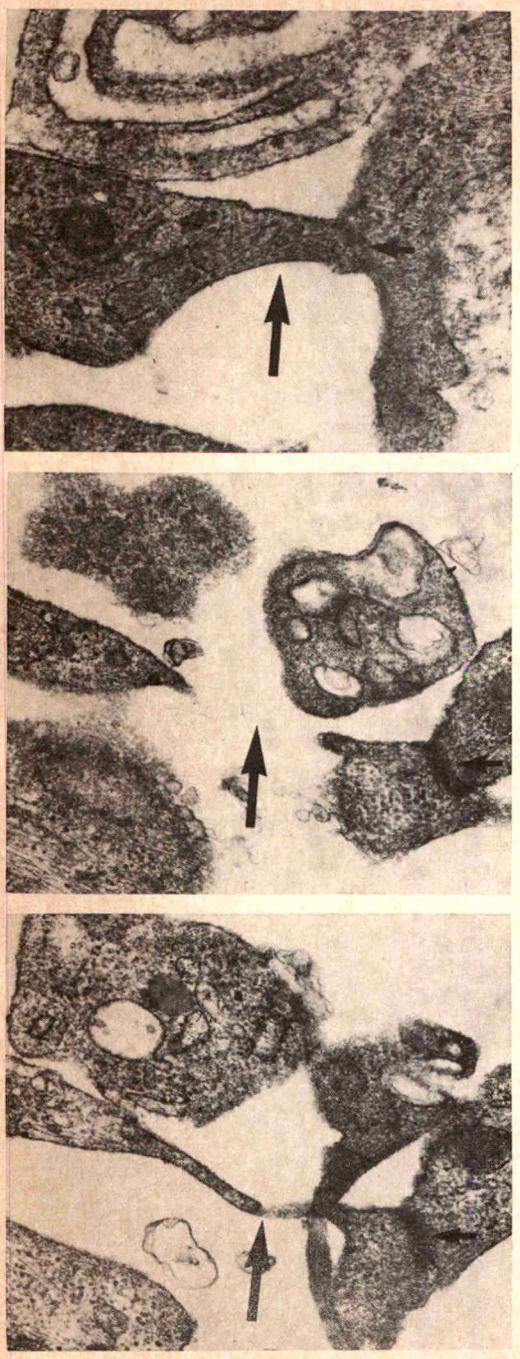


Fig. 14 (Grierson and Lee). Selected serial sections showing a nonvacuolar intracellular channel at 50 mm Hg (large arrows). The region of contact between two endothelial cells is indicated by smaller arrows (×41,000).

attenuated and in close apposition to the corneoscleral wall, minipores and distorted giant vacuoles were occasionally observed. Small giant vacuoles were present in the endothelium lining the septae, and less frequently on the corneoscleral wall or collector channels. Overall, however, there was less vacuolation than at 22 and 30 mm Hg.

A general feature of all endothelial cells lining the canal was that coated vesicles were virtually absent, there were fewer uncoated vesicles, and pinocytotic vesicles were not identified. Lysosomes and lysosomal complexes were evident, particularly in the endothelium lining the trabecular aspect of the canal.

Discussion

Alteration of the pressure differential across the endothelium lining Schlemm's canal has shown that significant changes occurred at the fine structural level in the pinosomes, micropinosomes, giant vacuoles, and the nonvacuolar transcellular channels. The active process of micropinocytosis in the endothelial cells lining the trabecular aspect of Schlemm's canal has been implicated in the transfer of aqueous humor across the endothelial monolayer by functioning as a respiratory-dependent component of bulk outflow.[2-7] The hypothesis was reinforced by the demonstration of electron-dense tracers, after their injection into the anterior chamber, in some of the micropinocytotic vesicles on both the meshwork and canal aspects of the endothelial cells.[2,4,5,7] As such, the micropinocytotic activity was thought to resemble the transendothelial fluid transport (cytopempsis) described by Palade[28] in capillary endothelia. In addition, Fine[2,3] considered that the larger vesicles formed from marginal folds (and also found in capillary endothelia[26]) may be another means of active transcellular passage of aqueous humor. On the other hand, the significance of respiratory-dependent vesiculation in the transport of aqueous humor has not been fully established since

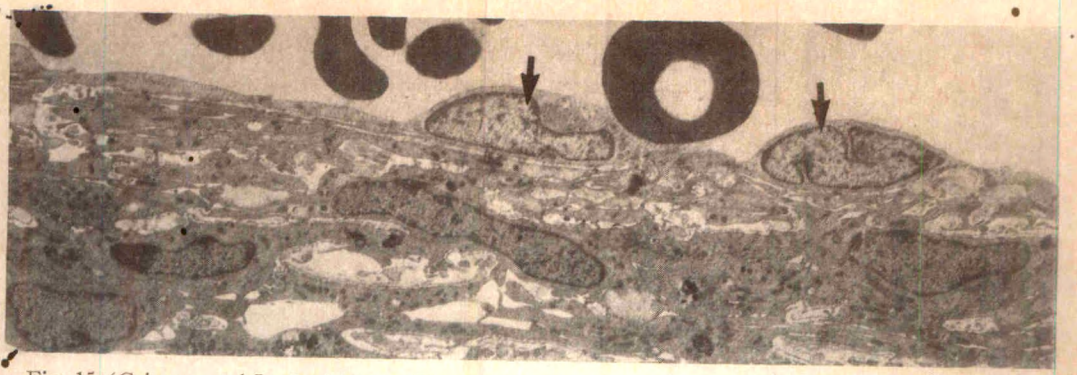


Fig. 15 (Grierson and Lee). At 0 mm Hg no giant vacuoles are present in the endothelium and only an occasional perinuclear bulge (arrows) interrupts the regularity of the endothelium (×3,200).

several authors,[8,23,29,30] who used electron-dense tracers, considered it unlikely that micropinosomes were greatly involved in the transfer of tracer elements across the endothelium.

In the present experiment, the response produced by intraocular pressure change on pinocytotic and micropinocytotic activity was unexpected. We anticipated that, as the processes were respiratory-controlled transport systems, they would be pressure independent and that vesicle numbers would remain relatively constant throughout the pressure range. A possible explanation for the inverse relationship between intraocular pressure and vesicle incidence may be the variations in the amount of proteinaceous material within Schlemm's canal at the various pressures. At 0 and 8 mm Hg, the canal contained flocculent material (thought to be coagulated plasma proteins) and red blood cells, while at higher pressures (22, 30, and 50 mm Hg) the canal lumen was free from blood. If the increased number of vesicles was related to the reflux of blood into the canal lumen, the changes in activity would be more prevalent on the luminal surface and involve all the endothelial cells lining the canal and this was the case.

Certainly, in other tissues, micropinocytotic activity within cells appears to depend to some extent on the composition of the surrounding medium. Smooth micropinosomes have been implicated in the transcellular transport of macromolecules in capillary endothelia[31-33] and the close relationship between macromolecules on the surface coat of the endothelium and micropinosome formation has been emphasized.[32] Coated vesicles are involved in protein uptake into some specialized cell types[34,35] and this process can be stimulated by an increase in the protein content of the surrounding fluid.[35] Similarly, the formation of large pinocytotic vesicles can be induced in peritoneal macrophages by the presence of calf serum and also many complex organic molecules.[36-38] However, the process of pinocytosis involving endothelial flaps can be exaggerated by immersion fixation,[39] so that the striking increase in the numbers of pinocytotic vesicles observed at 0 mm Hg may be due, in part, to a fixation artifact.

Although the findings indicate a relationship between plasma concentration and the incidence of micropinocytotic and pinocytotic vesicles, we are uncertain about the significance, function, and directional movement of these respiratory-dependent transport vesicles in the endothelium lining Schlemm's canal. Despite the uncertainties, it is unlikely that in the normotensive state, the vesicles are either primarily involved in, or play a major role in, the bulk outflow of aqueous humor.

The observed increase in the number and size of the giant vacuoles over the pressure range of 0 to 30 mm Hg confirms the previ-



Fig. 16 (Grierson and Lee). Closer examination of the endothelial cells at 0 mm Hg shows that micropinocytotic activity is prevalent particularly on the canal surface of the cell (×56,000). Insets, Both show part of the apical surface of other endothelial cells. Coated vesicles are indicated by arrows. The coated type of vesicle was prevalent and the surrounding membrane complex had a distinctive striated appearance (×64,000).

ous observation[1] by light microscopy and scanning electron microscopy on the same experimental tissue. In addition, examination of the fine structure of the vacuolar structures showed that they are lined by a continuous membrane and since the endothelial cell morphology is well preserved, the possibility that the vacuoles are artifacts due to inadequate fixation seems unlikely. This argument is supported by the observation that giant vacuoles were not observed at a pressure of 0 mm Hg, an experimental situation in which the primary fixation technique was the least satisfactory and in which autolytic degenerative changes were most likely to occur.

Examination of isolated sections showed that some giant vacuoles had membrane-lined pores. The pores occurred more frequently on the meshwork aspect of the vacuolar structures and these meshwork pores were generally larger than the less frequently observed lumen pores. Indeed, meshwork pores were found throughout the pressure range of 8 to 30 mm Hg, whereas lumen pores were not found at 8 mm Hg. Serial reconstructions provided information that explained the distribution of pores seen in random section at 22 and 30 mm Hg, most giant vacuoles had a meshwork pore, a small group had a lumen pore in addition to the meshwork pore, and an equally small group had a lumen pore only. On no occasion was a totally intracytoplasmic vacuole identified, an observation that confirmed previous studies by serial reconstruction.[8,10-12] Since giant vacuoles with lumen pores formed a small proportion of the vacuole population, it is not surprising that they were not found in the endothelium maintained at 8 mm Hg when vacuoles were scarce.

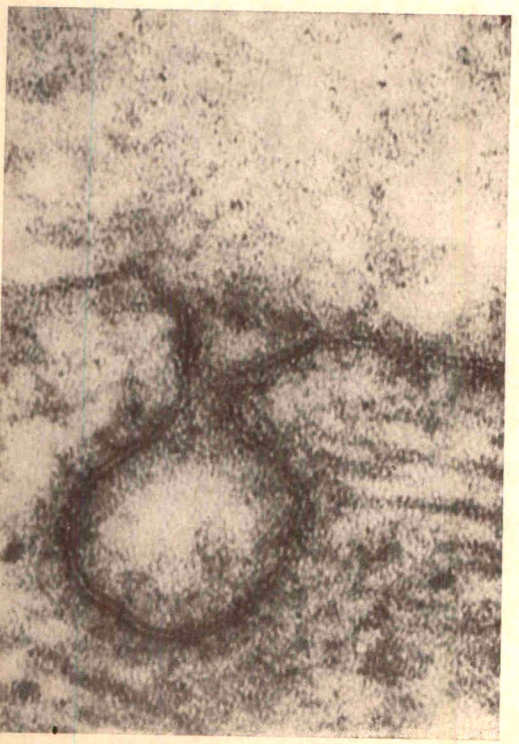


Fig. 17 (Grierson and Lee). A coated vesicle on the luminal aspect of an endothelial cell lining the trabecular position of Schlemm's canal at 0 mm Hg. The tissue was stained en bloc with uranyl acetate and the trilaminar nature of the vesicular limiting membrane is obvious. An osmiophilic material is present on both the luminal and cytoplasmic leaflets of the limiting membrane (×220,000).

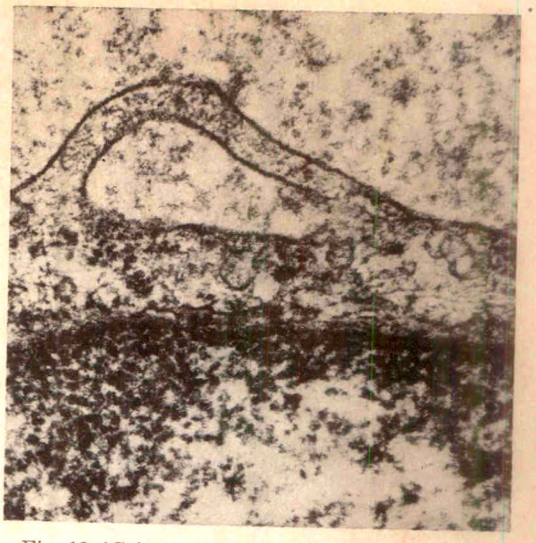


Fig. 18 (Grierson and Lee). A pinocytotic vesicle, formed from a cytoplasmic projection, on the luminal aspect of an endothelial cell lining the trabecular aspect of Schlemm's canal. The vesicle is in the perinuclear region of the cell (×32,000).

Both the meshwork and lumen pores were larger and more easily identified at elevated (22 and 30 mm Hg) than at lower (8 and 15 mm Hg) intraocular pressures. The pore changes were either directly or disproportionately related to the increase in the size and numbers of giant vacuoles and we are trying to establish the nature of this relationship by a detailed quantitative analysis of pore incidence at the various pressures. What we have established, however, is that within the giant vacuole population, there were vacuoles with pores on both their meshwork and canal aspects and that these increased in number with increases in intraocular pressure.

Vacuoles of this type have been described in a variety of primate species[8,9,19-23,40] and it has been suggested that they may serve

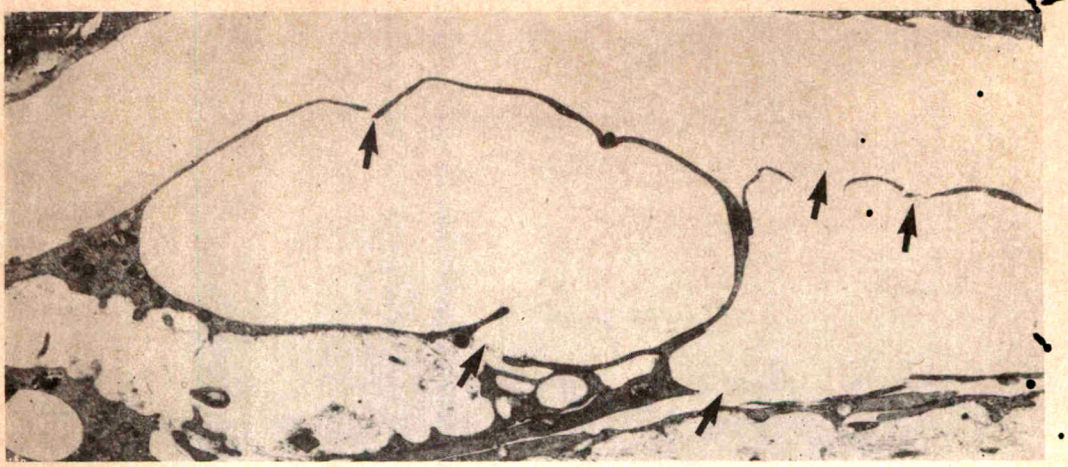


Fig. 19 (Grierson and Lee). The giant vacuoles at 50 mm Hg are large and appear spidery with frequent openings on both the canal and meshwork positions (arrows). Frequently these openings were more like tears or deficits rather than true pores (×6,400).

as transcellular channels for the passage of aqueous humor through the endothelium into Schlemm's canal. Tripathi[23,41] proposed that the transcellular vacuolar channel represented a stage in a cyclical process that is initiated by an invagination from the meshwork surface; the invagination then expands, forms a transcellular channel, and eventually collapses. The primary factors influencing the vacuolation process were thought to be the pressure gradient across the endothelial monolayer and an unspecified inherent or peculiar property of the cells that made them pressure-sensitive. He suggested that energy consumption was unlikely to play a major role in vacuolation because only a moderate amount of energy-producing organelles were present in the endothelial cells. In our experimental model, we tested some of the assumptions in the hypothesis.

Although vacuolation increased pari passu with the increase in intraocular pressure from 0 to 30 mm Hg, there was no obvious change throughout the pressure range, in either the glycogen content, the ribosomal content, or the numbers and size of the mitochondria, so that there is no evidence to indicate that energy consumption or protein production was necessary to increase the vacuole population in the endothelium. The apparent anomaly is explained if the vacuoles are considered to be deep invaginations of the cell surface rather than cytoplasmic organelles. The vacuolation process would then be a progressive distortion of the cell (that is, it does not involve extensive membrane production), which is a response to hydrostatic pressure and is opposed by the natural elasticity of the endothelial cell. Endothelial pliability probably depends on cytoplasmic microfilaments, which in our investigation were found in intimate contact with the vacuolar membrane. Conceivably, if the microfilaments have contractile properties, these structures may be involved in the initial invagination process.

The enlarging vacuole causes attenuation of the cytoplasm toward the canal surface but the mechanisms of pore formation are not fully understood. A possible precursor of the lumen pore may be the small fenestration or minipore previously described by Wulle[9] and Inomata, Bill, and Smelser[8] and which we have shown here to become increasingly prevalent in attenuated endothelium. It would seem likely that a fenestration appears after the endothelium of the giant vacuole had reached a critical thinness and it would thus establish a region of weak-

ness in the stretched outer shell of the vacuole. After the formation of the canal pore the vacuole-like invagination constitutes a transcellular channel through which fluid, tracer materials,[8,23,29] and even cells[8,23] may pass.

If the cyclical nature of the vacuolation process is to be accepted, an explanation must be provided for the mechanisms which could lead to the eventual collapse of the vacuole. The most likely factor is a reduction in the net inflow below the level required to maintain patency of the vacuolar channel. Vacuolar collapse, therefore, may be produced by the active constriction of the meshwork pore, but as this would involve the expenditure of cellular energy, this explanation is not easily acceptable. It is more likely that vacuolar collapse is a passive process. For example, the effective diameter of the meshwork pore could be reduced by a mechanical valve-like action of the underlying cellular and extracellular elements, which were often found in close association with these openings. If the meshwork elements were drawn toward the meshwork pore with the general movement of fluid to and then through the transcellular channel, transendothelial flow would be eventually blocked. Alternatively the collapse could be initiated primarily by changes in flow dynamics rather than by alterations to vacuolar morphology. With a faster transendothelial flow than that through the loose connective tissue (endothelial meshwork[42,43]) beneath the lining endothelium, the pressure differential across the channel would decrease due to insufficient filling of the subvacuolar space. As this implies that the resistance to aqueous flow offered by the endothelial meshwork is an important factor in the vacuole cycle, the close relationship between dilatation of the endothelial meshwork and vacuolar incidence is worthy of emphasis. This relationship appears to operate only within the physiologic range, because at 50 mm Hg the numbers of giant vacuoles were reduced over the markedly distended endothelial meshwork. In this circumstance, the outflow was probably nonphysiologic because the anterior part of the canal was often occluded, cellular separation was apparent in the endothelial monolayer, and the giant vacuoles were damaged.

Our study helps to explain some of the controversies that have arisen concerning the nature of the giant vacuoles. Shabo, Reese, and Gaasterland[16] showed that spontaneous pressure-independent vacuolation occurred in the endothelium lining Schlemm's canal when fixation was delayed for 30 minutes after death. They suggested that all giant vacuoles were a postmortem artifact produced by poor or delayed fixation, because vacuoles were rarely seen when immediate fixation via the episcleral veins was employed. However, retrograde perfusion reverses the natural direction of fluid flow, so that, in view of the pressure-dependent nature of the invagination-vacuolation process, the findings are not surprising. We maintain that intracameral fixative perfusion at a controlled pressure is the method of choice. Although fixative penetration may be slower by the intracameral route than by the aqueous veins, the penetration follows the direction of aqueous flow at physiologic rates. In addition to Shabo, Reese, and Gaasterland,[16] others[3,12] have shown that vacuolar structures are more evident in the tissue after delayed fixation, but these vacuolar structures were not confined to endothelium lining the trabecular wall,[3,12,16] and were not pressure-dependent[16]; in one paper they were described as being totally intracytoplasmic.[12] These important differences from the invagination-vacuoles we described suggest that postmortem vacuoles are probably separate entities.

However, Johnstone and Grant[44] demonstrated by light microscopy that pressure-dependent vacuolation occurred in postmortem eyes. Since postmortem vacuoles are pressure-independent, we assume that the vacuoles described by Johnstone and Grant[44]

were invagination-vacuoles possibly involved in outflow, but there is no reason why these invaginations should not develop in cells whose viability is questionable provided that the cells retain elasticity and that property[23,41] that allows them to invaginate. Indeed, pressure-induced vacuolation would be a less plausible outflow system if it did not occur in vitro given the similarities in outflow dynamics in living and postmortem eyes.[45-47]

Nonvacuolar gaps in the endothelium lining the trabecular aspect of the canal were intracellular channels in the control (15 mm Hg) tissue. Since the channels were absent at lower pressures and their incidence increased to 30 mm Hg, they also appear to be (like giant vacuoles) temporary, pressure-sensitive structures that may serve as an outflow route for aqueous humor. At 30 mm Hg, not all of the gaps were intracellular channels, because some were the result of mechanical separation of adjacent endothelial cells so that an accurate assessment of the increase in nonvacuolar channels was difficult. Being pressure-sensitive and restricted to the regions where the endothelium is narrow, the dynamics of the nonvacuolar channel may be essentially similar to that of the vacuolar channel, differing only in the part of the endothelial cell in which the structure is formed. Thus, in a thicker part of the endothelium, aqueous humor transfer necessitates vacuole formation, but in narrower areas a smaller nonvacuolar channel is sufficient.

Although we concentrated almost exclusively on the intracellular passage of aqueous humor, several authors have considered intercellular routes to be significant. Fluid outflow through openings between neighboring endothelial cells[5-7] and seepage through the intercellular clefts[4,16] received the most attention. Our findings show that cellular separation was observed only at 30 and 50 mm Hg and was probably produced by mechanical disruption. It is likely that separations of this type are not a natural feature of the normotensive endothelium.

Since the intercellular clefts appeared to be sealed by continuous tight junctions or zonula occludens,[4,8,9,23,29] this was considered a relatively minor exit pathway. Recently, the occluding nature of the junctions was confirmed by using uranyl acetate en bloc staining,[16,48] but Shabo, Reese, and Gaasterland[16] concluded that the junctions were discontinuous (maculae) and were not continuous belts surrounding the endothelial cells (zonulae). The discontinuities between the tight junctions were thought to be a possible exit route for aqueous humor. However, the junctions between the endothelial cells appear to have little mechanical strength since they can be disrupted by eyeball[23] massage, by paracentesis,[49] and, as shown by us and Svedbergh,[50] by excessively elevated intraocular pressures; so for this reason, these discontinuities could be mechanical separations. Even if the small intercellular pores are not artifacts it has been suggested[51] that they are of insufficient size and frequency to account for more than a small proportion of bulk outflow.

Although inter- and intracellular passage of aqueous humor need not be mutually exclusive (since a dual system of outflow may be in operation), the bulk of the available evidence suggests that most fluid passage occurs by transcellular rather than intercellular pathways.

Summary

In a transmission electron microscopic investigation of the endothelium lining Schlemm's canal subjected to graded levels of intraocular pressure (0 to 50 mm Hg for one hour), there was an increase in the number of vacuolar structures with the increase in pressure (range, 8 to 30 mm Hg). At 0 mm Hg, giant vacuoles were absent, while at 50 mm Hg their numbers were less than at 22 and 30 mm Hg. Vacuoles were invaginations either from the meshwork or from the canal surface of the endothelium. A few were transcellular channels that possibly served as a pressure-sensitive outflow

system. In addition, the numbers of nonvacuolar transcellular channels and minipores increased with an increase in pressure while the numbers of pinocytotic and micropinocytotic vesicles decreased. The changes were not accompanied by alterations in organelles associated either with protein or energy production. At 50 mm Hg, breaches in the endothelium lining the trabecular wall were obvious and aqueous outflow was considered to be by nonphysiologic routes.

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SPONTANEOUS REGRESSION (AUTOINFARCTION) OF PROLIFERATIVE SICKLE RETINOPATHY

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Spontaneous regression of proliferative retinopathy is well documented in diabetes mellitus[1,2] and retrolental fibroplasia,[3,4] although the factors responsible for such vascular involution are not known.[5] Davis[6] studied the role of vitreous detachment in proliferative diabetic retinopathy and found that complete vitreous detachment may result in regression of retinopathy with fewer hemorrhages and disappearance of many new vessels. Our initial experience[7] suggested that spontaneous regression of new vessels (sea fans) was extremely rare in proliferative sickle retinopathy. Although Okun[8] and later Condon and Serjeant[9] showed isolated cases of what we now consider to be autoinfarcted retinal sea fans in sickling diseases, the concept of autoinfarction has never been stressed in this disease.

SUBJECTS

Of 365 patients who were screened, 152 patients were observed periodically (every six to 12 months). Forty-five patients had proliferative sickle retinopathy (stages III, IV, and V).[7] Each of these patients had a detailed fundus drawing, fundus photography, and fluorescein angiography. Of these 45 patients, nine (20%) showed autoinfarction of retinal sea fans.

In one patient, sea fan infarction occurred twice during the period of observation. In the others, autoinfarction had apparently occurred before our first examination. Patients were 13 to 55 years of age with an average age of 31.2 years. The age range of the nine patients with autoinfarction of retinal sea fans was 26 to 54 years with an average age of 39.2 years. The difference of years between the two averages suggests a fairly long interval during which sea fans were actively perfused. However, we observed autoinfarction that occurred within two days (Case 1). Of these patients, 25 were male and 20 female; five men and four women had spontaneous involution of proliferative sickle retinopathy.

Most patients with proliferative sickle retinopathy had sickle cell hemoglobin C disease (SC) and sickle cell anemia (SS) (Table). Of those patients with autoinfarction of sea fans, eight had hemoglobin SC disease, and one had sickle cell thalassemia (Sthal).

CASE REPORTS

Case 1—A 26-year-old black woman with hemoglobin SC disease was seen in 1972 because of vit-

TABLE

HEMOGLOBIN ELECTROPHORESIS OF PATIENTS WITH PROLIFERATIVE SICKLE RETINOPATHY* AND SPONTANEOUS REGRESSION

Hemoglobin Type†	Patients with PSR	Patients with Spontaneous Regression of PSR
AS	2	0
AC	1	0
SS	9	0
SC	29	8
Sthal	4	1

* PSR indicates proliferative sickle retinopathy.

† AS indicates sickle cell trait; AC, hemoglobin C trait; SS, sickle cell anemia; SC, sickle cell hemoglobin C disease; and Sthal, sickle cell thalassemia.

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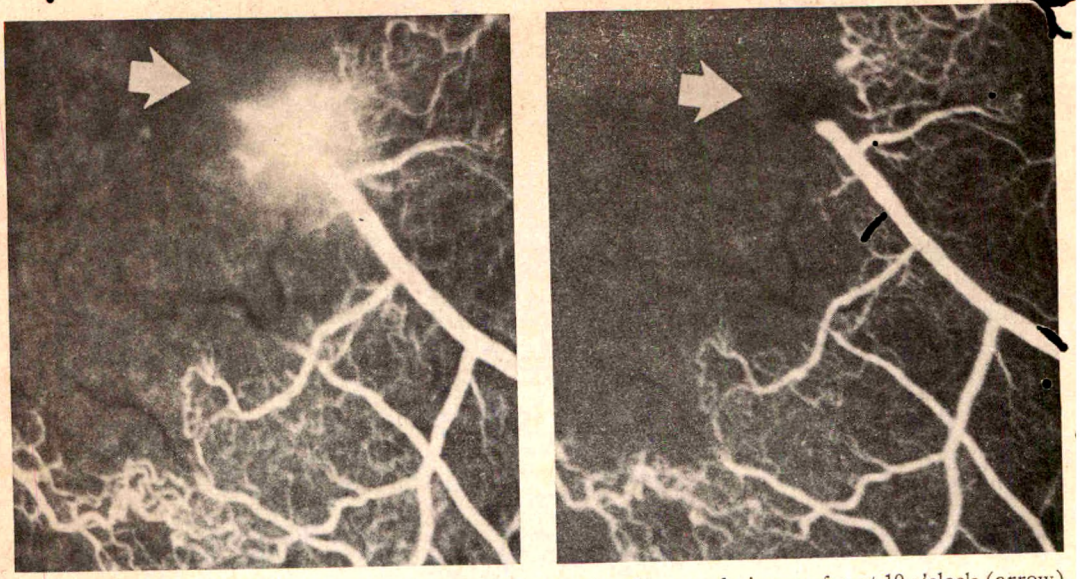


Fig. 1 (Nagpal and associates). Case 1. Left, Right eye showing a perfusing sea fan at 10 o'clock (arrow) on Feb. 27, 1974. Right, Same sea fan two days later shows no perfusion.

reous hemorrhage in the left eye. Visual acuity was R.E.: 20/20, and L.E.: 20/70. Slit-lamp examination of the anterior segment revealed conjunctival sickling signs and iris atrophy in both eyes. Ophthalmoscopy of the left eye revealed a recent vitreous hemorrhage with several sea fans in the equatorial retina; the right eye showed stages I and II of retinopathy.

The patient was followed at the clinic at regular intervals. On Feb. 27, 1974, two years after her initial visit, a new sea fan was noted at the 10-o'clock position (Fig. 1, left) of the right eye. This lesion was not treated but observed. Within two days, the sea fan autoinfarcted (Fig. 1, right); fluorescein angiography revealed nonperfusion of the sea fan. On June 21, a new sea fan (Fig. 2, left) was seen at the 9-o'clock position, which, six weeks later (Aug. 1), was autoinfarcted (Fig. 2, right). Fluorescein angiography showed no perfusion of this sea fan.

Case 2—A 30-year-old black woman with hemoglobin Sthal disease was seen in May 1974 with the

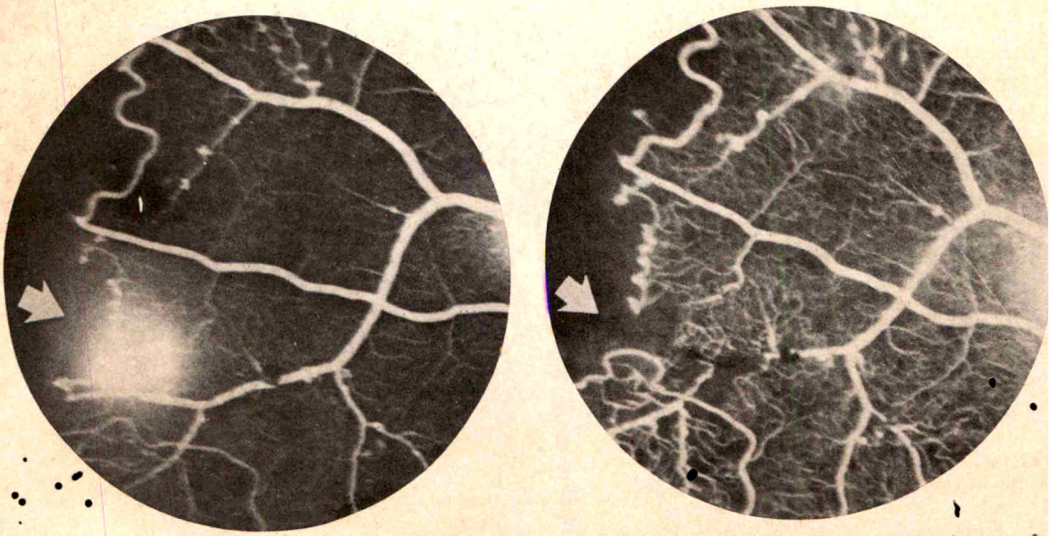


Fig. 2 (Nagpal and associates). Case 1. Left, 9-o'clock position of right eye shows a perfusing sea fa (arrow) in June 1974. Right, Six weeks later, the same sea fan shows no perfusion (arrow).

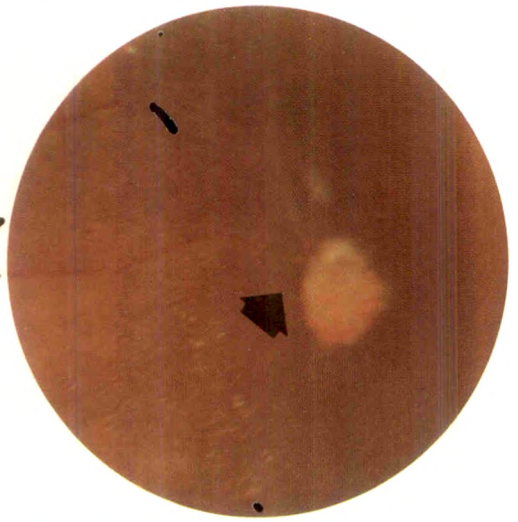


Fig. 3 A (Nagpal and associates). Case 2. Nonperfused (autoinfarcted) sea fan (arrow) is at 3 o'clock in the left eye.

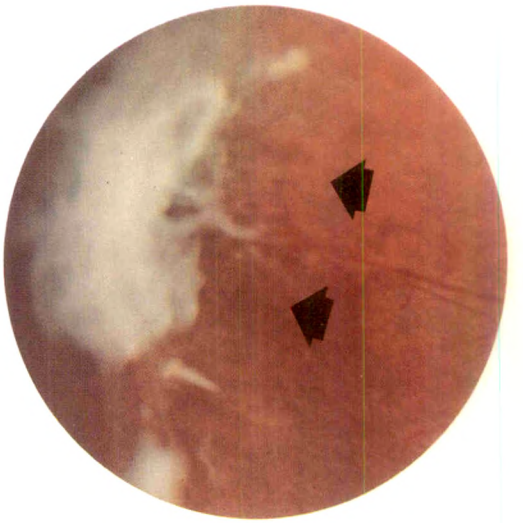


Fig. 4. A (Nagpal and associates). Case 3. Nonperfused (autoinfarcted) sea fan (arrows) is at 10 o'clock in the right eye.

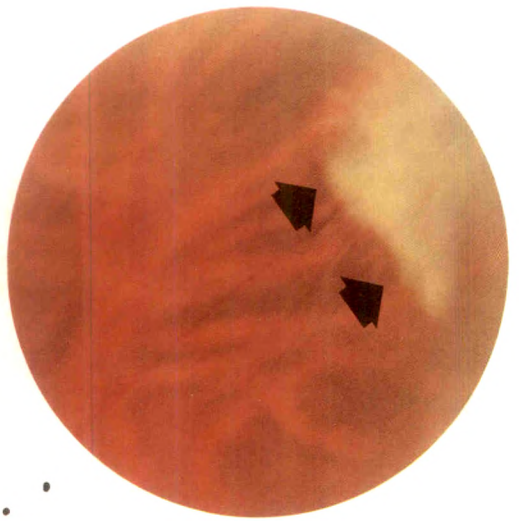


Fig. 5. A (Nagpal and associates). Large fibrous nonperfused (autoinfarcted) sea fan (arrows).

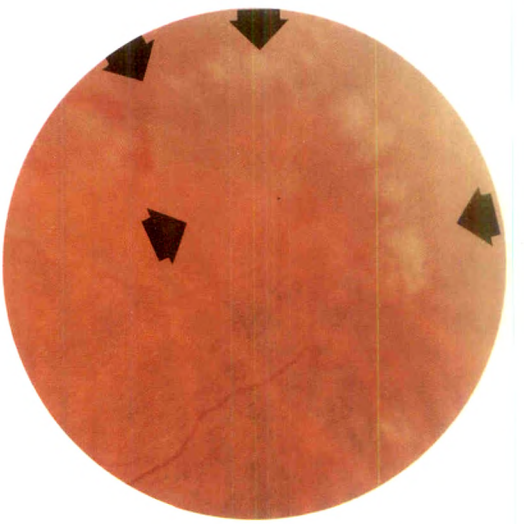


Fig. 6. A (Nagpal and associates). Case 8. Nonperfused (autoinfarcted) sea fan is at 1:30 o'clock in the left eye.

complaint of blurred vision in the left eye. Visual acuity was 20/20 in each eye. Fundus examination of the right eye showed peripheral arteriolar occlusions, avascular zones, and a small area of neovascularization at 7 o'clock at the equatorial region. Examination of the fundus of the left eye revealed sea fans at 12, 1, 2, and 3:30 o'clock in the equatorial region. The sea fan at 3:30 o'clock was the largest. By fluorescein angiography, both eyes showed perfusion and leakage from all the retinal sea fans in both eyes except from the 2-o'clock sea fan in the left eye (Fig. 3, A and B), which failed to show any filling. The sea fans in the left eye, except for the one at 2 o'clock, were treated with argon laser photocoagulation with successful closure of feeder vessels.

Follow-up examination in December 1974 showed occlusion and fibrosis of all the treated sea fans, and they had become white. The sea fan at 2 o'clock was still occluded, and it and its feeder vessels had fibrosed and become white.

Vitreous examination of the left eye showed posterior vitreous detachment with collapse, although vitreous humor remained adherent to all the sea fans. There was no vitreous detachment over the autoinfarcted sea fan that appeared elevated.

Case 3—A 29-year-old black man with hemoglobin SC disease was seen in January 1972. In 1965 he had bilateral loss of vision that gradually improved over several months.

In January 1972, visual acuity was R.E.: 20/25, and L.E.: 20/40. The conjunctiva revealed small comma-shaped vascular changes consistent with sickle cell disease. Ophthalmoscopic examination of the right eye showed two black sunbursts[7] at the equator at 12 o'clock, a fibrous sea fan at 10 o'clock at the equator, and two other small fibrous areas at 9 o'clock. Ophthalmoscopic examination of the left eye revealed a white fibrous sea fan at 3 o'clock and two black sunbursts at 4 o'clock. No fluorescein angiography was done at this time.

In October 1973, he had developed sea fans at 4 o'clock in the right eye and at 12 o'clock in the left eye. These sea fans showed leakage of dye on fluorescein angiography. Cryoapplication successfully closed the perfused sea fans in both eyes. The sea fan at 10 o'clock in the right eye was not treated because it showed no perfusion (Fig. 4, A and B).

In February 1974, the patient had recurrent vitreous hemorrhage in the left eye. A small sea fan at 2 o'clock in the right eye was successfully occluded with argon laser photocoagulation. The sea fan at 10 o'clock in the right eye remained unchanged. The vitreous hemorrhage in the left eye had gradually cleared and visual acuity was 20/40. No definite sea fans were found at this examination because of hazy media.

An examination of the vitreous body of the right eye showed posterior vitreous detachment without collapse. At the sea fans, vitreous humor was thick and adherent.

Case 4—A 42-year-old black woman, who had a vitreous hemorrhage in the left eye in 1953 that gradually cleared, had hemoglobin SC disease. In 1961 she had vitreous hemorrhages in the right eye that did not clear fully. The right eye became painful and blind and was enucleated in 1965. When she was seen in March 1975, visual acuity was 20/25-2 with −1.75 sphere. The conjunctiva showed a few isolated comma-shaped segments of vessels compatible with sickle cell disease. Slit-lamp examination showed iris atrophy at 12 o'clock. Ophthalmoscopic examination of the left eye revealed fibrous tissue proliferation over the disk and su-

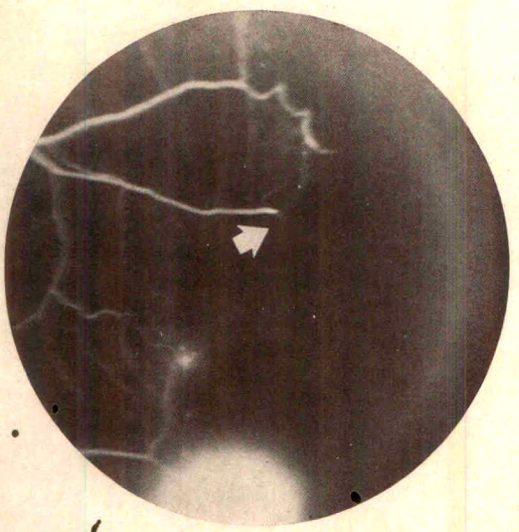


Fig. 3, B (Nagpal and associates). Case 2. Sea fan (same as in Fig. 3, A) shows no perfusion of dye (arrow).

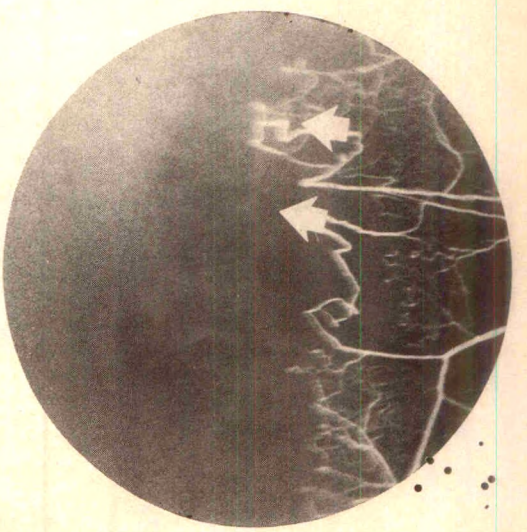


Fig. 4, B (Nagpal and associates). Case 3. Same area as in Figure 4, A shows no leakage of dye.

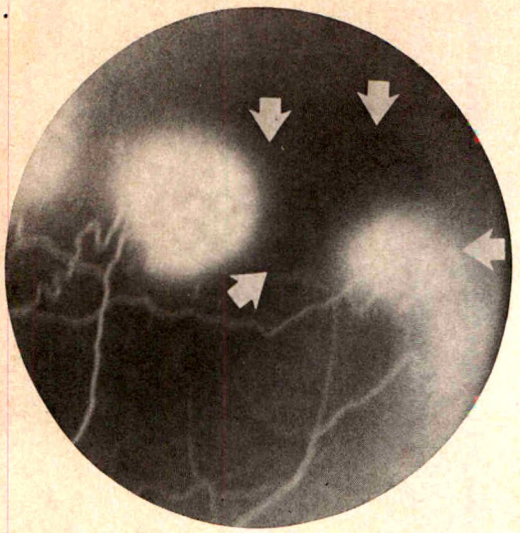


Fig. 5, B (Nagpal and associates). Case 5. There is no perfusion of dye from large fibrous sea fan while adjacent sea fans show leakage of dye.

perior to the disk extending above the macula. There was a black sunburst at 10 o'clock. Fibrous sea fans at 2 and 4 o'clock in the equatorial region appeared to be elevated above the surface of the retina.

On fluorescein angiography the retinal sea fan at 2 o'clock showed mild leakage of dye. The sea fan at 4 o'clock did not perfuse. In December 1974, there was mild perfusion of the retinal sea fan at 2 o'clock. Examination of the vitreous body showed a moderately rigid vitreous framework with condensed vitreous bands connecting two areas of tractional schisis involving superior temporal vessels near the disk and the sea fan at 2 o'clock. The vitreous was collapsed. There was a hole in the dense posterior vitreous face overlying the sunburst at 10 o'clock. The ring of vitreous humor that had been attached to the disk had detached and was pulled toward the area of schisis at 2 o'clock. The autoinfarcted sea fan was lying on the posterior vitreous face. No definite connection with feeder vessels was seen.

Case 5—A 50-year-old man with hemoglobin SC disease had a mature cataract in the right eye with no light perception in August 1974. Ultrasonography of this eye showed funnel-shaped total retinal detachment. Visual acuity in the left eye was 20/20 with a +0.75 sphere. Anterior segment examination was unremarkable. Examination of the fundus of the left eye showed a normal optic disk and macular region. The retinal periphery showed black sunbursts at 3 and 6 o'clock at the equator and multiple retinal sea fans at 12, 1, 2, and 4 o'clock. Between 1 and 2 o'clock there were four sea fans, one of which was large, fibrous, and raised above the retina. On fluorescein angiography all the retinal sea fans showed leakage, except the large fibrous sea fan at 1:30 o'clock (Fig. 5, A and B). This large fibrous sea fan had no connection to any retinal vessels. The leaking sea fans were successfully closed with argon laser photocoagulation. Examination of the vitreous body showed a large lake of vitreous fluid in the center of the vitreous cavity. There was posterior vitreous detachment, although the vitreous was adherent to the 12-o'clock sea fan and to the nonperfusing sea fan at 2 o'clock. We suspected that the vitreous body had adhered to other sea fans but no definite relationship was established.

Case 6—A 31-year-old black man from Nigeria with hemoglobin SC disease probably had his first vitreous hemorrhage in 1970. In December 197[illegible] the patient lost useful vision in the right eye, and in February 1974, he developed clouding of vision in the left eye. Visual acuity was R.E.: hand motions, and L.E.: 20/25, with mild sickle conjunctival signs in both eyes, extensive vitreous hemorrhage in the right eye, and sea fans in the left eye at 12, 4, 5, and 9 o'clock. We noted an autoinfarcted sea fan between 2 and 3 o'clock; fluorescein angiography confirmed nonperfusion. In February and May 1974, the sea fans at 12, 4, 5, and 9 o'clock were successfully treated with xenon arc photocoagulation.

The vitreous hemorrhage in the right eye settled with bilateral eye patching for 48 hours and elevation of the head of the bed to 45 degrees. Fluorescein angiography confirmed sea fans barely visible at 12 and 3 o'clock that were subsequently treated by triple freeze-thaw transconjunctival cryopexy. The vitreous body failed to clear over the next six months. In August 1974, vitrectomy via the pars plana was performed with successful clearing of vitreous. Subsequently a horseshoe tear in the right eye at 10 o'clock was treated by cryopexy. Examination of the vitreous body of the left eye showed collapse of the posterior vitreous with a thickened posterior vitreous face. The vitreous humor adhered to the inner surface of the elevated sea fan and to other sea fans.

Case 7—A 47-year-old black man with hemoglobin SC disease, seen in February 1973, had visual acuities of 20/20 in each eye. By ophthalmoscopy, the right eye had a normal optic disk and macular region, black sunbursts at 8, 11, 2, and 6 o'clock in the equatorial region, and elevated white fibrous sea fans at 8:30, 9:30, 10:30, and 4 o'clock. The feeder vessels to these sea fans were also white. The left eye had a normal disk and macular region, black sunbursts at 6 and 7 o'clock at the equator, and three elevated white fibrous sea fans at 9, 10, and 3 o'clock by ophthalmoscopy. The feeder vessels to the sea fans at 10 and 3 o'clock were white.

Fluorescein angiography of the right eye showed occlusion of retinal vessels in the periphery. None of the sea fans showed any perfusion with, or leakage of, the dye. In the left eye a sea fan at 3 o'clock did not perfuse, but sea fans at 9 and 10 o'clock showed profuse leakage of dye. In May 1974 the sea fans at 9 and 10 o'clock in the left eye were successfully treated by photocoagulation.

Examination of the vitreous body of the right eye showed posterior vitreous detachment with collapse, although the vitreous body adhered to the sea fans. In the left eye, there was posterior vitreous detachment with collapse and adherence of vitreous to the sea fans.

Case 8—A 50-year-old black man with hemoglobin SC disease was seen in August 1974 because of poor vision in the right eye. Visual acuity was R.E.: hand motions, and L.E.: 20/20. Anterior segment examination was unremarkable. An ophthalmoscopic examination of the left eye showed a black sunburst at 3 o'clock and multiple sea fans in the retinal periphery at 9, 11, 1, 3, 6, and 7 o'clock. Fluorescein angiography showed no leakage of dye at the sea fan at 1 o'clock (Fig. 6, A and B). The perfused sea fans were successfully treated by photocoagulation of feeder vessels.

Examination of the vitreous body showed posterior vitreous detachment with collapse of the vitreous body that adhered to the sea fans.

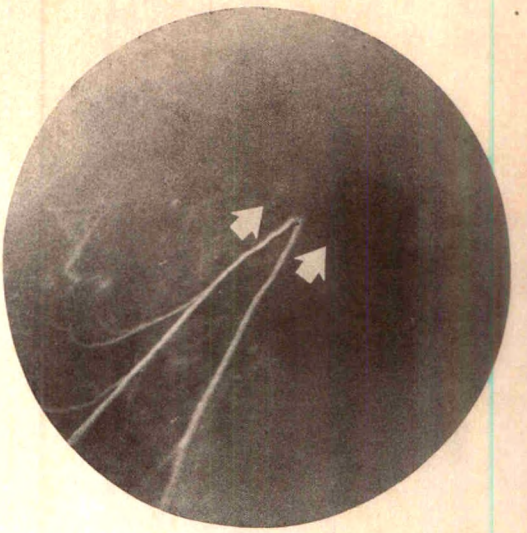


Fig. 6, B (Nagpal and associates). Case 8. Same area as in Figure 6, A shows no perfusion of sea fan.

Discussion

Autoinfarction of retinal sea fans in proliferative sickle retinopathy has not previously been documented to our knowledge, although isolated photographs of ostensibly autoinfarcted sea fans have been published.[8,9] Condon and Serjeant,[10] however, discussed the possibility of spontaneous regression. In our series, autoinfarction of retinal sea fans occurred in approximately 20% of patients with proliferative sickle retinopathy. Spontaneous regression of neovascularization, therefore, is not as uncommon as once was thought. Accordingly, the natural course of proliferative sickle retinopathy resembles that of proliferative diabetic retinopathy and of retrolental fibroplasia.

The mechanism of autoinfarction is poorly understood. Sea fans ordinarily occur at the most peripheral edge of the vascularized retina, at the junction of perfused and nonperfused areas. Progressive, centripetal retraction of the anterior vascular arcade of the peripheral retina, as seen in patients with sickle cell disease,[11] may lead to occlusion of feeder arterioles to the sea fan. This may result in permanent cessation of blood flow through the sea fan with subsequent thrombosis, organization, and fibrosis. Condon and Serjeant[10] reported a case in which feeder vessels had become white and occluded. There was whitening of the feeder vessels in some of our cases. Many sea fans probably undergo autoinfarction by this mechanism (Figs. 1 and 2).

Fluorescein angiography is required for confirmation of absent perfusion, because some silver wire arterioles actually contain blood, while others are nothing more than fibrotic cords. In treating sea fans with photocoagulation, we have often employed a feeder vessel technique in which nutrient arterioles (but not their dependent neovascular capillary beds) have been occluded. Infarction, atrophy, and permanent nonperfusion of the entire sea fan has been the usual result.

The role of vitreous detachment in spontaneous regression of proliferative diabetic retinopathy has been well studied.[2,6] Although vitreous abnormalities in sickle cell retinopathy have not been reported, vitreous changes may play a role in autoinfarction of sea fans. With progressive vitreous detachment and collapse, one of three things may happen. The vitreous body may detach from the retina and sea fan without affecting the sea fan, or vitreous humor may pull on the

sea fan, tearing the vessels and leading to hemorrhage about the sea fan or into the vitreous cavity. The third possibility is that the vitreous may pull on the sea fans and their feeder vessels, presumably causing hemodynamic alterations, sluggish flow, and occlusions in the feeder vessels.

Sometimes the sea fan may be pulled into the vitreous chamber so much that it loses its base and is torn free from its feeder vessels (Cases 4 and 5). The large fibrous sea fans in these two cases were elevated above the surface of retina and had no anatomic connection with retinal vessels. The sea fans were lying on the posterior vitreous face, and one of them moved freely with movement of the eye.

Although autoinfarction of retinal sea fans occurs in proliferative sickle retinopathy, withholding therapy in the hope of a spontaneous infarction is not without danger, because vitreous hemorrhages often occur in eyes with proliferative sickle retinopathy.[7,12] For example, we[7] have observed that the incidence of spontaneous vitreous hemorrhage increased from 28 to 44% in a group of patients observed for six to 77 months without ocular therapy. In view of acceptably low complication rates,[13,14] therapy of sea fans with an argon laser, xenon arc photocoagulator, or retinal cryoprobe is advocated before the onset of vitreous hemorrhage.

Summary

Of 45 patients with proliferative sickle retinopathy in stages III, IV, and V, nine patients (eight with hemoglobin SC disease, one with sickle cell thalassemia) showed spontaneous regression (autoinfarction) of retinal sea fans. One mechanism involved in autoinfarction of neovascular tissue is progressive, centripetal retraction of the anterior vascular arcade of the peripheral retina. In addition, vitreous traction on feeder vessels may result in sluggish blood flow and occlusion of these vessels, or may tear the sea fan completely away from its feeder vessels. In view of the many incidences of vitreous hemorrhages that occur in patients with proliferative retinopathy, however, we recommend treatment of neovascularization rather than prolonged observation.

Acknowledgment

Michael Goldbaum, M.D., referred a patient (Case 3).

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AMBLYOPIA SCREENING WITH RANDOM-DOT STEREOGRAMS

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In two recent reports Reinecke and Simons[1,2] reconsidered the validity of stereoscopic testing with regard to amblyopia screening. They pointed out that negative results in this respect[3,4] do not necessarily indicate the unreliability of stereoscopic screening, but may just as well reflect the shortcomings of the particular test employed.

The stereoscopic test most widely used for visual screening is the familiar Titmus Stereo test, particularly its screening plate, the Stereo Fly. The obvious reason for this is that this test was specially designed for testing children, and as such seemed to have few competitors that might do a better job. However, based on results obtained in a validation experiment, in which this test was administered to patients with known visual dysfunctions, Simons and Reinecke[2] correctly concluded that the Titmus test is too unreliable for amblyopia screening.

That this conclusion is not extendable to stereoscopic testing in general was convincingly demonstrated by Reinecke and Simons[1] when they reported screening results obtained with a new test for stereoscopic vision. The novel feature of this test is that it is based on the same principle as the well-known Julesz random-dot stereogram.[5] From the point of view of screening, a stereogram showing figures that are visible only in depth offers two distinct advantages when compared to the traditional stereoscopic tests. First, a random-dot stereogram, devoid of monocular depth cues, constitutes a foolproof test criterion. Second, it facilitates the response task, since the form of the test object has to be recognized rather than its location in depth. Thus, it provides new possibilities to circumvent the usual problems of communications that arise when screening young children.

The advantages of the random-dot stereogram are not merely putative, but were affirmed by the experiences obtained with a random-dot stereoscopic test of our own design. This test, the TNO test for stereoscopic vision, was made available commercially in Europe about two years ago. It was introduced in the United States in July 1974,* and it is not surprising, therefore, that the TNO test escaped the attention of Reinecke and Simons, particularly since the existence of this test has not been reported before in an international journal.[6,7]

Before the TNO test was introduced, a comparative validation study was conducted in which, as in the Reinecke and Simons study,[1] the Titmus test was used as a comparison. These old data, now having become actual again, lend further support to Reinecke and Simons' conclusion that the stereoscopic test is an ideal screening instrument for amblyopia or its promoting visual dysfunctions, provided the right test is used.

MATERIAL AND METHODS

The TNO stereoscopic test—The random-dot stereograms of the TNO test are prepared as anaglyphs, the familiar two-color stereoscopic pictures (usually red and blue-green) that evoke a stereoscopic depth perception when viewed through similarly colored spectacles. The spectacles supplied with the test come in two sizes—for testing children and adults—and are fitted with glass filters to prevent scratching of the material.

It sometimes has been assumed that

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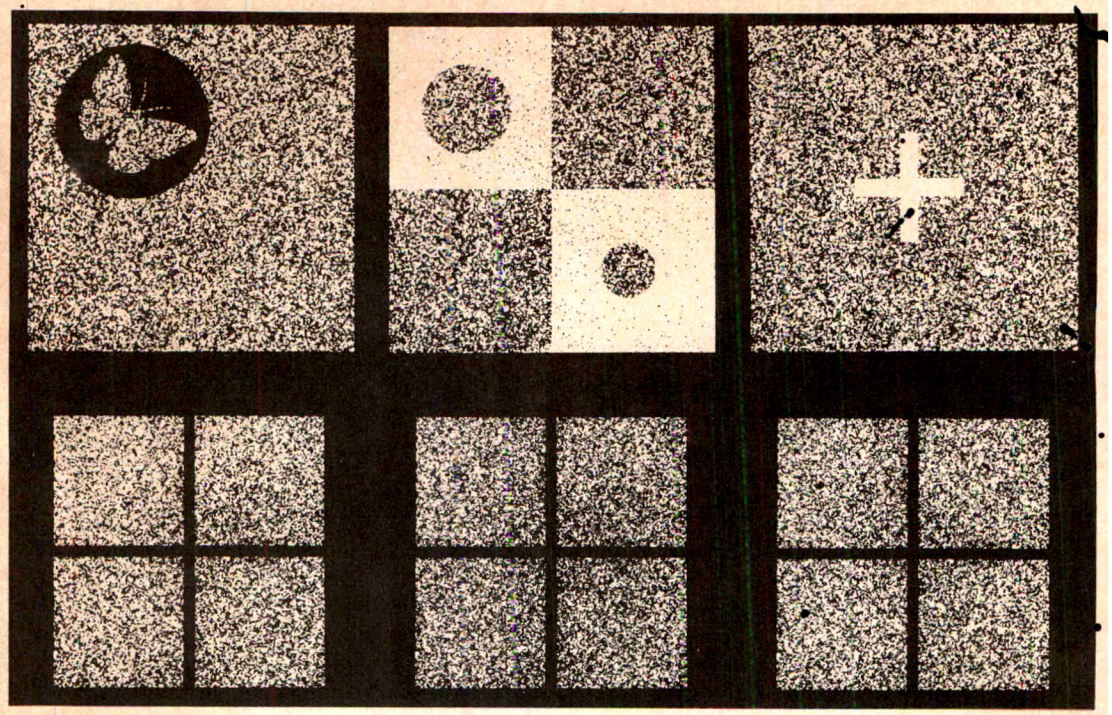


Figure (Walraven). Random-dot stereograms used in the TNO test for stereoscopic vision (only one half of each stereoscopic pair is shown). Top row, Screening plates containing concealed as well as visible figures. Bottom row, Quantitative plates comprising six different retinal disparities varying from 15 to 480 seconds of arc. Scale = 1 :4.2.

anaglyphs, as opposed to vectographs (the polarized stereoscopic pictures used in the Titmus test), may induce binocular rivalry, and hence, interfere with binocular fusion. Although this seems plausible, this assumption was never proved by using the TNO test. In these random-dot stereograms, rivalry was not experienced at all; the red-green random-dot texture was binocularly integrated into a single, almost neutral, color.

We produced the TNO test as a booklet, containing three screening plates (retinal disparity, 33 minutes of arc), three quantitative plates (retinal disparities ranging from 15 to 480 seconds of arc), and a suppression test. The six test plates are shown in the Figure (only one color separation of each stereoscopic pair is shown). Each of the screening plates contains at least one figure that always can be seen, besides concealed test figures, that is, binocularly visible only. A child who, due to a visual defect, is unable to respond to the hidden test figures is still able to respond to the visible figures. In this way the child is unaware of having failed the test and, consequently, does not try to cover up for a defect by guessing, or worse, refusing to cooperate. Moreover, the examiner obtains the important information: that the failure to respond to the hidden test figures was not merely due to a lack of communication.

In the first screening plate this principle was realized by means of two identical butterflies, one visible, the other invisible. The child was first invited to point at the visible butterfly, and then told that there were, occasionally, other butterflies to be seen. We then asked the child to point out the other butterflies, if possible.

In the second plate there were four disks (balls, saucers) that differed in size. Two of these, the largest and the second smallest,

were visible only in depth. The child was first asked to point at the smallest disk—this one was always visible—and then at the largest. The largest was hidden in the upper right corner of the test plate, but if it could be seen, the child pointed instead at the second largest that was situated in the upper left corner. Thus, the child had the opportunity to give a positive indication of defective stereoscopic vision, which is less ambiguous, of course, than no response at all.

In the third screening plate four hidden test figures—a disk, triangle, square, and diamond—were arranged around a visible central cross. On the page opposite the screening plate there was an example of all five figures. The child was instructed to look at the example, starting with the cross, and then to look for the appropriate figure in the test plate.

The three quantitative plates contained hidden figures only, since these were originally intended to be used for adults only. They are well suited for testing children too, although it may be necessary to show a picture of the test symbol first. Only one test symbol was used throughout—a disk with a 60-degree sector missing at one of four possible positions (that is, the same principle as used for the Landolt C and the illiterate E tests). In each plate these stereoscopic optotypes were shown at two depth levels, two at each level. The three plates comprised six different depth levels, which, when viewed from a distance of 40 cm, corresponded to retinal disparities of 480, 240, 120, 60, 30, and 15 seconds of arc, respectively.

Validation experiment—To compare the validity of the TNO and Titmus stereoscopic tests, both tests were administered to 81 children (2 to 7 years old) who were referred to the clinic because of suspected or already detected visual dysfunctions. Based on the clinical data (strabismus status, visual acuity, fusion, and suppression), this patient sample was subdivided into four categories—patient, potential patient, normal, and unclassified. With the exception of the latter category, consisting of a few children who did not cooperate on the tests, such a classification can never be strict. However, since a comparative rather than an absolute evaluation was intended, the exact composition of each category should be unimportant. The criteria were not significantly different from what is commonly used. All children designated as patients had visual acuities of the worse eye less than 0.7 (usually less than 0.5), associated with a constant tropia or anisometropia, or both. Potential patients had visual acuities of 0.7 or better, often associated with intermittent esotropia. Those considered to have normal or near normal vision had visual acuities of 0.8, or better and were orthophoric or had only weak phorias or intermittent exotropias.

Based on the results obtained with the TNO and Titmus stereoscopic tests, the patients were classified into four groups, using the following criteria: (1) failing to pass the screening plates (TNO) or Stereo Fly (Titmus) test; (2) passing the screening tests but not the quantitative tests at a retinal disparity of 240 seconds of arc (that is, the first quantitative plate of the TNO test) or 200 seconds of arc (that is, the No. 3 circle, or the rabbit of the Titmus test); (3) passing both the screening and quantitative test (at the required level); and (4) no response due to inability or unwillingness to cooperate on the tests.

The patients in these four categories were qualified as referrable, possibly referrable, not referrable, and unclassified, respectively. With the Titmus test it was not always possible to discriminate between the first two categories, because some children who passed the Stereo Fly test did not respond to the Circles test. In a real screening program these patients would be treated as not referrable because of the absence of any contraindication. Accordingly, they were also classified as such in the present study.

TABLE 1

DIAGNOSTIC CLASSIFICATION AND SCREENING RESULTS OF 81 CHILDREN (2 TO 7 YEARS OLD)

Diagnostic Classification*	Screening Results of TNO and Titmus Stereoscopic Test							
	Referrable		Possibly Referrable		Not Referrable		Unclassified	
	TNO	Titmus	TNO	Titmus	TNO	Titmus	TNO	Titmus
Patient (37)	30	26	7	5	—	2	—	4
Potential patient (12)	5	—	7	7	—	1	—	4
Normal (28)	—	1	2	3	25	23	1	1
Unclassified (4)	1	—	—	—	—	1	3	3

* Numbers in parentheses indicate total number of subjects included in each group.

We then determined to what extent the patient's referral status, as indicated by the stereoscopic test scores, was corroborated by the diagnostic classification. However, although the predictive power, or validity, of the tests can be evaluated, such an evaluation based on data obtained by professionals under ideal clinical conditions may not necessarily be representative of the screening efficiency of the tests under more realistic circumstances. Therefore, we compiled the results of a second experiment, in which the two tests were compared under less favorable conditions.

Screening in the classroom—The second experiment was conducted with 129 children (2 to 5 years old) at two locations, a nursery school and a day-care center. Originally, this experiment was initiated to check how well children would respond to stereoscopic screening. Only the screening plates were used, since it seemed unlikely that if children did not respond to these plates, they would respond to the more difficult quantitative plates. Furthermore, since the feasibility rather than the validity of stereoscopic screening was at stake, no subsequent ocular examination was performed. (The parents were notified in case of a negative test result, but no further steps were undertaken.) In retrospect, this seems unfortunate but these data are still useful for a comparative evaluation of the screening efficiency of the two tests.

Both tests were administered by one technical assistant who, although well experienced in testing procedures, had no clinical background that might enable him to assess the visual health status of the child. Thus, secondary cues as to the child's ability to see stereoscopically (strabismus, eye motility, fixation, and head tilting) could not influence the examiner's judgment, and hence, the screening efficiency of the tests.

RESULTS

Validation experiment—Eighty-one patients who were examined at the clinic were referred to the various diagnostic and screening classes (Table 1). At first glance there seems to be a fair degree of concordance between the two classifications. For instance, the 37 patients and 12 potential patients in this sample were all classified by the TNO test as either referrable or possibly referrable. Apparently, failure to pass both the screening plates and the first quantitative plate of the TNO test indicated amblyopia or its promoting visual dysfunctions.

The Titmus test was less effective in this respect. With this test, only 38 of the 49 (potential) patients were classified as such (78%). Of the 11 patients who were missed, three passed the Stereo Fly test. They probably would not have passed the Circles test, but since they did not cooperate on this test, they had to be qualified as not referrable. The other eight patients were missed be-

cause of lack of cooperation on any of the Titmus tests.

Only a few patients were overreferred, two by the TNO test and four by the Titmus test (Table 1). However, this may be a flattered result, due to the specific conditions of this experiment.

These results pertain to 2- to 7-year-old children. Considering the need for early treatment of amblyopia, however, a comparison of the two test performances in the lower age group of this sample would be more relevant. Evidence suggests that screening should preferably be performed before the age of 4.[3,8-10] Data pertinent to this age group are listed separately in Table 2.

In this group of 41 children, 26 potential patients were present who, as followed from the previous result, were all detected by the TNO test. The Titmus test, however, missed ten patients, resulting in the meager correct-referral score of 62%. Almost the same number (11) was missed in the case of the whole sample, so apparently the poor performance of the Titmus test is almost entirely due to its inadequacy for use with 2- to 4-year-old children.

Although the TNO test may still be used effectively in this age group, no wonders should be expected, considering that four patients (10% of this group) did not cooperate on the test. The other visual tests were no better, however, which suggests that this is the limiting age at which visual screening can be conducted. This conclusion was corroborated by the results of other screening studies. Oliver and Nawratzki[11] found visual acuity screening before the age of 3 to be of little value due to lack of cooperation on any test they tried (that is, picture charts, Snellen illiterate E, small toys, and matching tests). They were more successful when testing 3- to 4-year-old children, although the percentage of cooperative children still was not high (53%) when compared to results in the same age group in the present study (90%).

Screening in the classroom—Since we used no quantitative plates in this experiment, the subjects were classified only as referrable, not referrable, or unclassified. We distributed the subjects in these three categories, as found with the TNO and Titmus tests, respectively (Table 3). When comparing these data, a positive response on the TNO test is proof of the presence of stereoscopic vision. So, if a subject passes the TNO test, but not the Stereo Fly test, one knows for certain that the failure to pass the latter test was not due to the absence of stereoscopic vision. In other words, the subject in question is qualified as an overreferral of the Titmus test. Ten such patients were found (Table 3).

We are not certain that the same reasoning may be applied to the six patients who were qualified as not referrable by the

TABLE 2

DIAGNOSTIC CLASSIFICATION AND SCREENING RESULTS OF 41 CHILDREN (2 TO 4 YEARS OLD)

Diagnostic Classification*	Screening Results of TNO and Titmus Stereoscopic Test							
	Referrable		Possibly Referrable		Not Referrable		Unclassified	
	TNO	Titmus	TNO	Titmus	TNO	Titmus	TNO	Titmus
Patient (18)	15	12	3	—	—	2	—	4
Potential patient (8)	2	—	6	4	—	—	—	4
Normal (9)	—	1	2	—	6	7	1	1
Unclassified (4)	1	—	—	—	—	1	3	3

* Numbers in parentheses indicate total number of subjects included in each group.

TABLE 3

SCREENING RESULTS OF 129 CHILDREN (2 TO 5 YEARS OLD)

Titmus Test*	TNO Test		
	Referrable	Not Referrable	Unclassified
Referrable (15)	1	10	4
Not referrable (100)	6	93	1
Unclassified (14)	2	8	4
Total	9	111	9

* Numbers in parentheses indicate total number of subjects included in each group.

Titmus test, but as referrable by the TNO test. Possibly, these cases pertain to children with a low stereoscopic acuity who were just able to pass the Stereo Fly test (retinal disparity, 50 minutes of arc), but not the TNO screening plates (retinal disparity, 33 minutes of arc). Furthermore, a positive response on the Stereo Fly test does not necessarily indicate the presence of stereoscopic vision because of the strong monocular depth cues present. However, there are no clinical data available that allow a decision in this respect. And, since a positive response is generally more reliable than a negative response—the latter may be due to lack of cooperation—we gave the Titmus test the benefit of the doubt. Consequently, the six patients in question are considered as overreferrals of the TNO test, which still compares favorably to the ten definite overreferrals found with the Titmus test.

In a strict screening program, unclassified patients should also be referred, particularly since children often prefer not to respond at all when, due to a visual defect, there actually is nothing to respond to. The result of such a procedure is that the TNO and Titmus tests, respectively, refer 18 and 29 children (that is, the sum totals of referrable and unclassified cases in Table 3). Most of these referrals are overreferrals on subsequent examination. At least 18 children qualify as such with the Titmus test since they gave positive responses on the TNO test (Table 3). The TNO test overreferred seven children, that is, 60% less than the Titmus test. Naturally, this conclusion applies only to the results obtained under the specific conditions of this study. These results are not unrealistic, however, as suggested by the percentage of referrals (including overreferrals) found with the TNO test (15%) compared to that reported in various visual screening studies.[12,13]

DISCUSSION

The results of this study, corroborated by the findings of Reinecke and Simons,[2] leave little doubt as to the usefulness of the random-dot stereogram for visual screening. The specific advantages are the reliability of the positive test response, and the many possibilities for creating an intelligible response task. The latter property has been thoroughly exploited in the TNO test, resulting in three screening plates that provide the examiner with as many different approaches for procuring a test response. Therefore, children cooperated more frequently on the TNO test than on the Titmus test, particularly in the lower age range.

The comparatively low efficiency of the Titmus test was due not only to lack of cooperation but also to the fact that the test criterion of the screening plate, pinching or touching the wing of the Stereo Fly test, is not foolproof. Children with normal stereoscopic vision often did not give the appropriate response, perhaps because they feared to touch the Fly at all, or because of insufficient motor control. This probably explains the many overreferrals found in the screening experiment in the classroom (Table 3).

The Titmus test overreferred four patients (5%) in the sample tested at the clinic, whereas it overreferred at least ten children (13%) in the sample tested in the classroom. This difference in screening efficiency is partly attributable to the difference in composition of the two samples. The children tested at the clinic consisted mainly of patients with visual dysfunctions (60%), so even if the test referred all children, the percentage of overreferrals never would exceed 40%; this percentage is compared to an estimated 95% in a sample taken from a normal population. Besides a difference in sample composition, the difference in test conditions should also be considered. Overreferrals are not expected when a highly trained examiner has foreknowledge of the patient's visual dysfunctions. Then, the incidence of overreferrals cannot be used as a criterion for test performance except, of course, on a comparative basis.

The occurrence of underreferrals is, in principle, less susceptible to the "examiner effect." Barring the possibility that the examiner inadvertedly gives away the correct response on the test, an underreferral only results as a consequence of either an intrinsic ambiguity of the response task or invalidity of the test criterion. In the TNO test, the possibility of ambiguity is discarded because of the unequivocal response criterion of the test. The results of the validation experiment speak for themselves: the classification not referrable was never contraindicated by the clinical findings (Table 1).

The Titmus test, in contradistinction, underreferred three patients. This is a fair result when compared to the findings of Simons and Reinecke,[2] who found more underreferrals. As these authors pointed out, however, this may be attributed to patients utilizing the nonstereoscopic alignment cue to the correct response. Considering the higher average age of their sample group (13% less than 4 years old), such a prevalence of artifactual stereoscopic responses seems plausible.

In the present study this cognitive factor apparently was much less effective, probably due to the generally lower age of the subjects (50% less than 4 years old, and none older than 7 years). Lack of cooperation on the Titmus test, particularly to the quantitative plates, seems to be the major cause for the unsatisfactory performance of this test. The TNO test was more dependable with respect to the screening plates and the quantitative plates. Even in the 2- to 3-year-old age group, children discriminated retinal disparities as low as 120 seconds of arc, whereas in the 3- to 4-year-old range, thresholds of 60 seconds of arc were not exceptional.

Summary

A stereoscopic test was developed for the visual screening of preschool children. The TNO test for stereoscopic vision utilized the same principle as the Julesz random-dot stereogram, and provided a simple and unequivocal test criterion understood even by young children.

The results of a comparative evaluation of the TNO and Titmus stereoscopic tests proved the TNO test to be the more reliable of the two, particularly in the 2- to 4-year-old age range. Failure to pass this test at the 240 seconds of arc disparity level yielded an excellent screening criterion, as attested by the results of a validation experiment employing 81 patients (2 to 7 years old) with known visual health records. Furthermore, the screening results obtained from 129 preschool children (2 to 5 years old), tested in the classroom by a nonprofessional examiner, suggest that, under these more realistic conditions, the TNO test yields at least 60% less overreferrals than the Titmus test.

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Ophthalmic miniature

It is one of our problems that as we become crowded together, the sounds we make to each other, in our increasingly complex communication systems, become more random-sounding, accidental or incidental, and we have trouble selecting meaningful signals out of the noise. One reason is, of course, that we do not seem able to restrict our communication to information-bearing, relevant signals. Given any new technology for transmitting information, we seem bound to use it for great quantities of small talk. We are only saved by music from being overwhelmed by nonsense.

Lewis Thomas, *The Lives of a Cell. Notes of a Biology Watcher*
Viking Press, 1974

HORIZONTAL SACCADIC VELOCITIES IN DUANE'S SYNDROME

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Since Duane's[1] review of 54 cases of retraction syndrome, little has been added to our understanding of the etiology of this entity. Not until ocular electromyographic techniques were applied did the causes for the abnormal eye movements seen in the retraction syndrome become apparent.[2-9] Generally, medial rectus muscle activity was normal while lateral rectus muscle innervation was abnormal.[7,8] Co-contraction of the lateral rectus muscle with adduction and, at times, co-contraction of the superior and inferior rectus muscles with adduction[7] account for the retraction of the globe and the characteristic eyelid fissure changes.

Various authors[3,5-7,10] have emphasized that an understanding of the muscle firing pattern in Duane's retraction syndrome (that is, paradoxical innervation) assists in surgical planning. Active force tests (by holding the eye during attempted movement) are also accurate in telling which muscles are pulling abnormally during gaze movements with the normal eye. However, both electromyography (EMG) and active force tests are limited to cooperative teenagers or adults. Electro-oculography (EOG), a test that can be used with children and relatively uncooperative adults, was used to measure horizontal saccadic velocity in patients with Duane's retraction syndrome.

From the Smith-Kettlewell Institute of Visual Sciences and Department of Ophthalmology, Pacific Medical Center, San Francisco (Drs. Metz and A. Scott), and the Department of Ophthalmology, State University of Iowa, Iowa City, Iowa (Dr. W. Scott). This study was supported by grants EY 00299 and EY 01186, National Institutes of Health; National Institute of Neurologic Diseases grant NF 03354; and The Smith-Kettlewell Eye Research Foundation.

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MATERIAL AND METHODS

Duane's syndrome was diagnosed in 33 patients when[8]: (1) limited abduction was associated with retraction on adduction in 28 patients (Type 1), (2) exotropia with good abduction was associated with limited adduction and retraction on adduction in three patients (Type 2), and (3) limited abduction and adduction were associated with retraction on adduction in two patients (Type 3).

Horizontal ocular saccades were measured by EOG using a Beckman RS dynograph with modified rectilinear ink writers, dynograph amplifier (type 462), preamplifier (type 461-B), direct nystagmus coupler (type 9859), and nystagmus velocity coupler (type 9841). Miniature skin electrodes (Beckman) were placed nasal to the medial canthus, temporal to the lateral canthus, and the indifferent electrode centrally over the brow.[11] Saccadic amplitude varied between 20 and 40 degrees, depending on the size of the horizontal movement that the patient could make. Most movements were from the midline to a nasal position as most of the patients had significant limitation of abduction. In those patients who could rotate their involved eye lateral to the midline, movements were measured beyond the primary position. Selected patients also had ocular EMG performed, as described in an earlier report.[12]

Our series of 33 patients with Duane's syndrome consisted of 22 (67%) females and 11 (33%) males. Duane's syndrome was found bilaterally in five patients

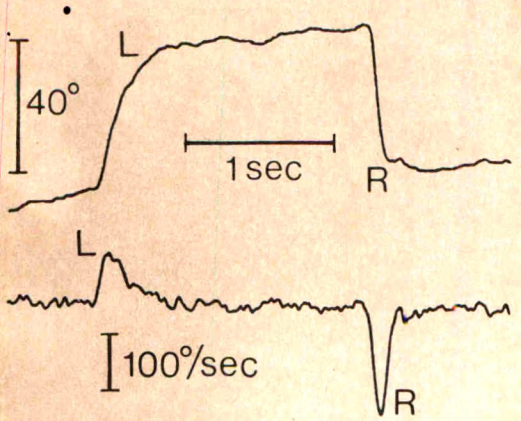


Fig. 1 (Metz, Scott, and Scott). Electro-oculogram of patient with Type 1 syndrome, left eye. Upper channel depicts eye position. Lower channel is a velocity channel. Saccades left (L) to abduction are slow and measure 100 degrees/sec. Saccades right (R) to adducton are fairly rapid and measure 200 degrees/sec.

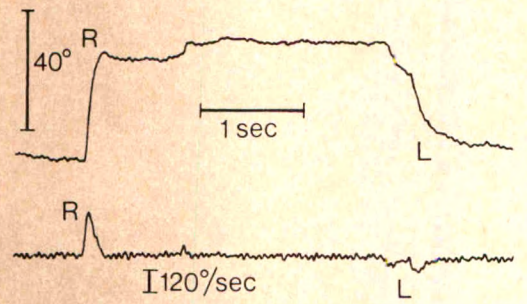


Fig. 2 (Metz, Scott, and Scott). Electro-oculogram of patient with Type 1 syndrome, left eye. The upper channel is an eye position channel while the lower channel is a velocity channel. Saccades left (L) to abduction are slow and measure 125 degrees/sec. Saccades right (R) to adduction are only mildly reduced in velocity and measure 180 degrees/sec.

(15%), in the right eye alone in seven patients (22%), and in the left eye alone in 21 patients (63%). In the primary position, there was no deviation in eight patients (24%), exotropia in six patients (18%), and esotropia in 17 patients (58%).

Results

Using the EOG technique, the range of normal saccadic velocity for 20 to 40 degrees amplitude saccades was 200 to 320 degrees/sec, with an average of 250 degrees/sec. These determinations were made from more than 300 records of patients with normal rectus muscle function (H.S.M., unpublished data).

Type 1 syndrome—In 28 patients with Type 1 (Table 1, 32 eyes), the average abduction saccadic velocity was 87 degrees/sec with a range of 45 to 160 degrees/sec. The average adduction saccadic velocity was 152 degrees/sec with a range of 70 to 200 degrees/sec (in only one eye was the adduction saccadic velocity less than 110 degrees/sec and in only one eye was it greater than 190 degrees/sec) (Figs. 1-3).

Type 2 syndrome—In three patients with Type 2 (four eyes), the average abduction saccadic velocity was 203 degrees/sec with measurements over 200 degrees/sec in three of the four eyes tested. The average adduction saccadic velocity was 104 degrees/sec (Fig. 4).

Type 3 syndrome—In two patients with Type 3, abduction saccadic velocity was 63 degrees/sec while adduction saccadic velocity was 113 degrees/sec (Fig. 5).

Ocular EMG was performed in ten pa-

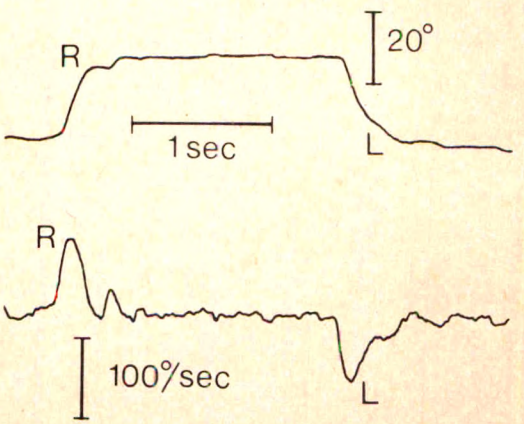


Fig. 3 (Metz, Scott, and Scott). Electro-oculogram of Type 1 syndrome, left eye. Upper channel is the eye movement channel while the lower channel is a velocity channel. Abduction movements to the left (L) are slow measuring 70 degrees/sec. Adduction saccades to the right (R) measure 100 degrees/sec and are moderately to markedly reduced in velocity.

tients. Of these, seven had Type 1, two had Type 2, and one had Type 3. The medial rectus muscle firing pattern in all patients was normal. The lateral rectus muscle in all patients either recruited or did not shut off on adduction. Normal inhibition of the lateral rectus muscle was not seen in any case. In Types 1 and 3, the lateral rectus muscle either failed to fire or failed to show recruitment on attempted abduction. In Type 2, lateral rectus muscle firing with attempted abduction appeared normal.

A separate group of 12 patients with Type 1 were studied. In the uninvolved eye, normal abduction saccadic velocities averaged 312 degrees/sec while normal adduction saccadic velocities averaged 343 degrees/sec. In the eye demonstrating the Duane's syndrome, abduction saccadic velocity averaged 150 degrees/sec and adduction saccadic velocity averaged 219 degrees/sec. As in the larger group of patients studied, abduction saccades were slow and adduction saccades moderately reduced in velocity when compared to the normal values.

Discussion

As expected, there was a marked decrease in abduction saccadic velocity in the most common type of Duane's syndrome, Type 1. This is explained by the EMG evidence of lack of firing or lack of recruitment of the lateral rectus muscle on attempted abduction. Numerous studies agree with these EMG findings.[2-4,6-10,13]

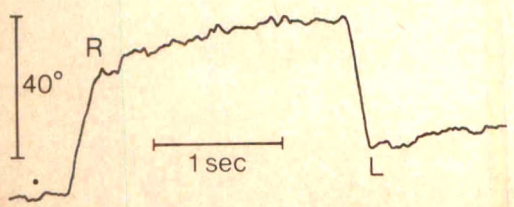


Fig. 4 (Metz, Scott, and Scott). Electro-oculogram of patient with Type 2 syndrome, left eye. Only the eye movement channel is represented. Abduction saccades to the left (L) measures 215 degrees/sec and are rapid. Adduction saccades to the right (R) measure 125 degrees/sec, and are moderately slowed.

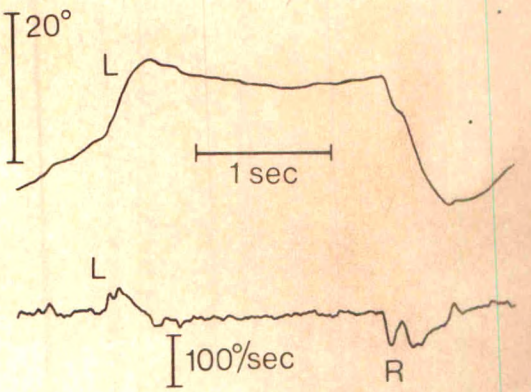


Fig. 5 (Metz, Scott, and Scott). Electro-oculogram of patient with Type 3 syndrome, left eye. Upper channel represents eye position while lower channel represents velocity. Abduction saccades to the left (L) measure 45 degrees/sec and are slow. Adduction saccades to the right (R) measure 60 degrees/sec and also are slow.

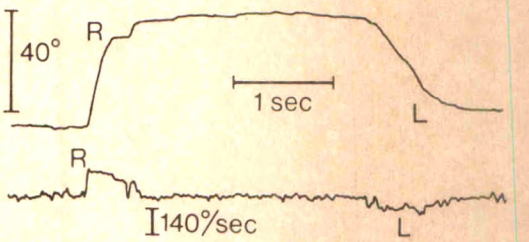


Fig. 6 (Metz, Scott, and Scott). Electro-oculogram of patient with Type 1 syndrome preoperatively. Upper trace represents eye position while lower trace represents velocity. Abduction saccades to the left (L) are slow and measure 40 degrees/sec. Adduction saccades to the right (R) are moderately slow and measure 140 degrees/sec.

Adduction saccadic velocities were moderately decreased. The lower limit of normal for horizontal saccades exceeding 20 degrees in amplitude is about 200 degrees/sec here and in other laboratories.[14]

In patients with sixth nerve palsy[11] or lateral rectus muscle restriction, adduction saccadic speed is normal. Ocular EMG[2,3,6-10,13] indicates that the medial rectus muscle recruits and inhibits normally in Duane's syndrome. The cause for reduced adduction saccadic velocity in Duane's syndrome is, therefore, the paradoxic innervation of the lateral rectus muscle on attempted adduction. The slowing of adduc-

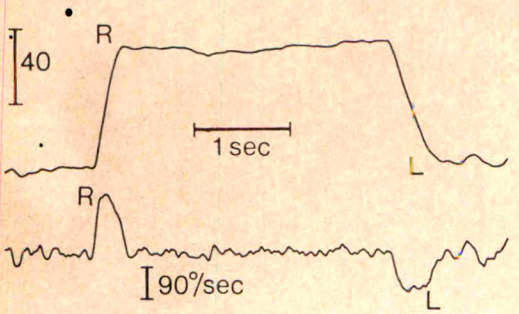


Fig. 7 (Metz, Scott, and Scott). Electro-oculogram of patient with Type 1 syndrome, left eye, postoperatively after a left lateral rectus muscle recession for exotropia (same patient as in Fig. 6). The upper channel represents eye position while the lower channel represents velocity. Abduction saccades to the left (L) remain slow and measure 55 degrees/sec. Adduction saccades to the right (R) are more rapid than preoperatively, now measure 240 degrees/sec. This increase in adduction saccadic velocity is likely due to the mechanical weakening of the paradoxically innervated left lateral rectus muscle.

tion saccades in a patient with limited ability to abduct the eye differentiates Duane's syndrome from lateral rectus muscle palsy. Although this differentiation can usually be made on clinical grounds with ease, we have seen two patients where EMG and saccadic velocity confirmed the diagnosis of Duane's syndrome in the presence of ambiguous clinical findings.

The importance of identifying anomalous co-contraction of the lateral rectus muscle has been stressed by Blodi, Van Allen, and Yarbrough,[4] and Pabst and Esslen.[5] They suggest that an exact knowledge of the innervational behavior of the horizontal rectus muscles is necessary before planning an operative procedure. With a lateral rectus muscle palsy, the lateral rectus muscle may be safely resected or advanced. In Duane's syndrome, significant advancement or resection of the lateral rectus muscle produces no improvement of abduction or increased retraction of the globe on adduction, and may lead to a lateral movement of the eye on attempted gaze to the opposite side (the "splits").

One of our patients with Type 1 Duane's syndrome had an exotropia when fixing in the primary position. Abduction saccadic velocity was 45 degrees/sec while adduction saccades averaged 140 degrees/sec (Fig. 6). After a lateral rectus muscle recession for the exotropia, abduction saccades remained slow and essentially unchanged. However, adduction saccadic velocity improved to 240 degrees/sec (Fig. 7). In all likelihood, the recessed lateral rectus muscle (which had been contracting on adduction, resulting in a reduction in adduction saccadic velocity), now had less of an effect in slowing adduction saccades because of its posterior insertion in the globe.

In our patients with rapid abduction saccadic velocities (Type 2), lateral rotation was good, and an EMG study showed the lateral rectus muscles recruited with abduction, consistent with both good lateral rotation and rapid abduction saccadic speed.

Various horizontal rotation anomalies resembling Duane's syndrome may follow head trauma. These include sixth nerve palsy, third nerve palsy with aberrant regeneration, and medial orbital wall fracture with tissue entrapment. Sixth nerve palsy may be differentiated by the lack of retraction of the globe on adduction and by normal adduction saccadic velocities. Aberrant third nerve regeneration after third nerve palsy demonstrates full abduction with rapid abduction saccades and slow adduction saccades, resembling the findings in Type 2. However, the patients with Duane's syn-

TABLE 1

AVERAGE SACCADIC VELOCITY*

Duane's Syndrome, Type	No. of Eyes	Adduction Velocity	Abduction Velocity
1	32	152	87
2	4	104	203
3	3	113	63

* Velocity measured in degrees per second. Velocities are means taken from five measurements in each patient. The mean values from each patient were averaged. The range of variation in each patient was within ±10% of the mean value.

drome do not usually show limitations of vertical eye movements or anomalous eyelid elevation on attempted downgaze (pseudo-Graefe's sign) as may frequently be observed with aberrant third nerve regeneration. Traumatic medial wall fracture of the orbit with tissue entrapment may give a clinical picture resembling Duane's syndrome.[15] Retraction of the globe and narrowing of the palpebral tissue were most marked in abduction. A previous study of a patient with traumatic medial wall fracture with tissue entrapment[16] indicated that the medial saccades were normally rapid. This is clearly different from the reduced adduction saccadic velocity noted in Duane's syndrome.

When abduction saccadic velocity is slow, the lateral rectus muscle is not actively pulling the globe into abduction. Therefore, a medial rectus muscle recession for esotropia will result in a relatively smaller amount of correction and may need to be increased to between 6.0 and 7.0 mm. Reduced adduction saccadic velocity is an indicator of co-contraction of the lateral rectus muscle. If the lateral rectus muscle is resected in an attempt to improve esotropia, medial rotation will be limited and enophthalmos on adduction will be worsened.[17] In Duane's syndrome with exotropia, lateral rectus muscle recession not only improves the exotropia but can improve the range of adduction and reduce the retraction of the globe on adduction.[7,18]

This is not to imply that all or most patients with Duane's syndrome require muscle surgery. Many patients are straight in the primary position or have only small angle deviations that are adequately compensated by a small degree of head turn. Muscle surgery is usually not required in these cases.[17] Our criteria for strabismus surgery are either a cosmetically noticeable ocular deviation or a cosmetically apparent head turn.

We summarized the findings in the three types of Duane's syndrome in terms of the deviation in primary position, ocular rotations, retraction on adduction, horizontal saccadic velocities, and the lateral rectus muscle EMG findings (Table 2).

Summary

Horizontal ocular saccadic velocities were measured by electro-oculography in 33 patients with Duane's syndrome. In 28 patients with limited abduction associated with retraction on adduction (Type 1), abduction saccadic velocity was markedly reduced while adduction saccades were moderately slow. In three patients with exotropia and good abduction but associated limited adduction and retraction on adduction (Type 2), abduction velocity was good,

TABLE 2

Summary of data*

Duane's Syndrome, Type	Deviation in Primary Position	Rotations		Retraction on Adduction	Saccadic Velocity		Lateral Rectus Muscle EMG	
		ADD	ABD		ADD	ABD	ADD	ABD
1	Significant ET	++	−	−	+	−	−†	−
1	Significant ET	+	−	+	−	−	+	−
3	Significant ET	−	−	++	−	−	++	−
1	Orthophone, not a problem							
2	Significant XT	−	+	++	−	+	+	+

* Minus sign indicates decreases from primary position; plus sign, increases from primary position; double plus sign, marked increase from primary position; XT, exotropia; ET, esotropia; ADD, adduction; and ABD, abduction.

† The EMG of the lateral rectus muscle decreased somewhat in adduction but did not shut off as it would normally.

while adduction saccadic speed was slow. In two patients with limited abduction and adduction with retraction on adduction (Type 3), abduction and adduction saccadic velocity was appreciably slow. Ocular electromyographic testing in selected patients indicated that slow abduction saccades could be explained by absence of lateral rectus muscle recruitment, while slow adduction saccadic speed could be explained by paradoxical innervation of the lateral rectus muscle.

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RING SCOTOMATA IN FUNDUS FLAVIMACULATUS

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In 1965, Franceschetti[1] reported 36 cases of fundus flavimaculatus, an ocular entity that he had described and named in 1962. Whereas this inherited dystrophy of the posterior part of the eye may be associated with macular degeneration and decreased visual acuity, the visual fields generally have been considered to be normal or to show only central scotomata in advanced cases.[1,2] We report six cases of fundus flavimaculatus in which complete or partial ring scotomata were associated with normal or near normal central visual acuity. To the best of our knowledge, ring scotomata have not been reported previously in association with this heredofamilial retinal disorder.

CASE REPORTS

Case 1—A 63-year-old man was first seen here in January 1971, complaining of "blind spots" that had progressed for two years, in both eyes. Visual acuity was 20/25 in each eye. Mild bilateral endothelial guttate changes of the cornea and delicate anterior subcapsular lens opacities were present, but did not interfere appreciably with vision. Ophthalmoscopic examination demonstrated fleck-like lesions considered characteristic of fundus flavimaculatus (Fig. 1, top). In addition, vague areas of pigment rarefaction were noted around the macular retinas of each eye. Formal testing of the visual field demonstrated bilateral incomplete ring scotomata (Fig. 1, bottom). Fluorescein angiograms demonstrated transmission defects through the rarefied pigmented epithelium and patchy areas of focal fluorescence corresponding with some but not all of the clinical lesions. Early in the study, some of the subtle, indistinct flecks fluoresced brightly and faded with time. Other flecks, more distinct, appeared to fluoresce only around their peripheries, whereas some of the most distinct and sharply outlined flecks obscured background fluorescence and did not light up at any time during angiography. For 3½ years, no demonstrable change in visual acuity developed, although the patient experienced enlargement of his scotomata.

Case 2—A 38-year-old white man was seen here in May 1971, with complaints of poor vision for two years. Visual acuity was R.E.: 20/40, and L.E.: 20/80. He had fundus lesions considered to represent fundus flavimaculatus with macular involvement (Fig. 2, top left). Visual fields showed dense ring scotomata bilaterally (Fig. 2, right). In a telephone interview with the patient three years

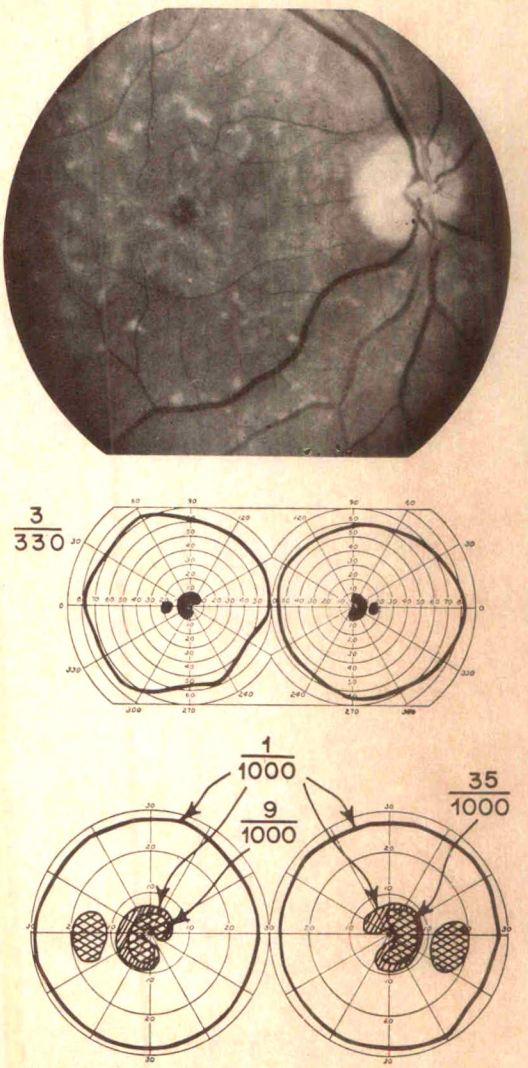


Fig. 1 (Passmore and Robertson). Top, Right eye showing flecked lesions characteristic of fundus flavimaculatus. Some derangement of pigment around the macular region can be seen. Bottom, Visual fields demonstrating incomplete ring scotomata dense to 35/1,000 white target on right and 9/1,000 white target on left. Visual acuity, 20/25 in both eyes.

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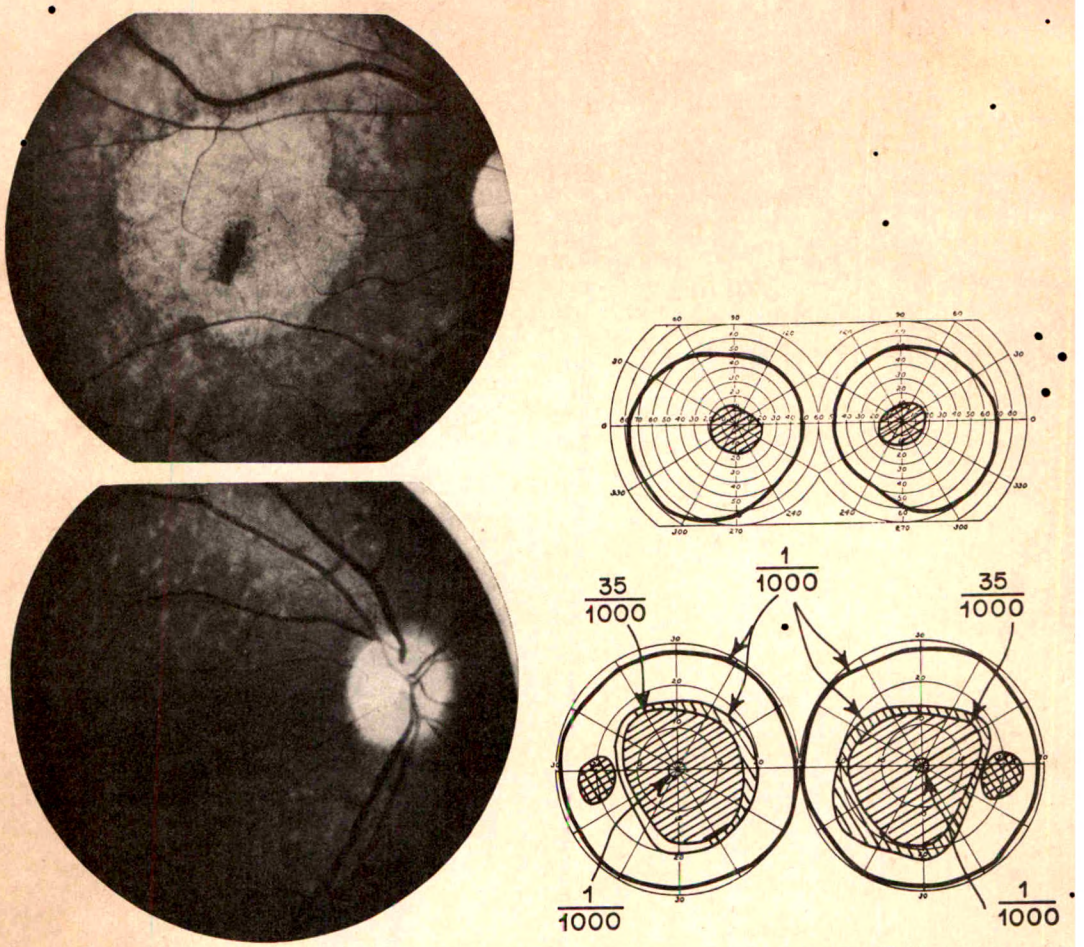


Fig. 2 (Passmore and Robertson). Top left, Right eye showing lesions of fundus flavimaculatus and severe abnormality in macular region. Bottom left, Right eye of sister shows macular and posterior polar lesions consistent with fundus flavimaculatus. Right, Visual fields show ring scotomata dense to 35/1,000 white target. Visual acuity was R.E.: 20/40, and L.E.: 20/80.

later, he indicated the blind spots had enlarged and he was no longer able to read the newspaper or to drive an automobile.

The patient's 39-year-old sister had similar ophthalmoscopic findings but more characteristic of fundus flavimaculatus and showing less evident pigment derangement in the macular regions (Fig. 2, bottom left). Her only symptom was a disturbance in color vision of one year's duration. Although color vision was not tested, visual acuity and visual fields were normal.

Case 3—A 30-year-old white man was seen in February 1972, complaining that letters had seemed fuzzy for three years. Visual acuity in both eyes was 20/25. Examination of the fundus revealed lesions characteristic of fundus flavimaculatus with mild macular involvement (Fig. 3, top). Bilateral ring scotomata were demonstrated on visual field testing (Fig. 3, bottom).

Electro-oculography and dark-adaptation studies showed normal results, as did the summated electroretinographic response to white light. Fluorescein angiography demonstrated dotlike transmission defects within a perimacular ring whose outside dimension was about 2 disk diameters. These hyperfluorescent dots were densely packed but not confluent. Peripheral to this ring were focal areas of fluorescence corresponding to the more indistinct yellowish flecks that were visible clinically and in the color photographs.

Case 4—A 38-year-old white man, first seen here in April 1973, complained of poor night vision of about two years' duration and of difficulty reading with the left eye for one year. He had failed the color vision test for a Federal Aviation Administration examination two years previously but he recalled easily passing the color vision test on his army induction physical several years earlier. Gen-

tral visual acuity was R.E.: 20/20, and L.E.: 20/30. Most of the H-R-R color plates were not recognized on color vision testing. An examination of the fundus showed changes characteristic of fundus flavimaculatus with macular lesions that appeared as atrophic, sharply delineated areas with a gray metallic sheen. The choroidal pattern, though more visible through these lesions than through the surrounding areas, nevertheless, was incompletely seen, indicating less than total atrophy of the pigment epithelium (Fig. 4, top left). The visual fields showed bilateral ring scotomata (Fig. 4, bottom left).

Approximately six months after his initial visit, the patient noticed a decrease in the visual acuity in his left eye and 11 months later, visual acuity was 20/300. Visual acuity and visual field of the right eye had not changed appreciably from those on the initial examination.

On initial examination, fluorescein angiograms showed slight hyperfluorescence irregularly distributed around the macular areas. This was not clearly correlated with visible clinical lesions. Additionally, in both macular areas, there were some sharply delineated, plaque-like areas of hyperfluorescence corresponding with those clinical lesions that evidenced the metallic sheen. These areas did not appear to be associated with peripheral dye diffusion, but within their boundaries, fluorescence in several pinpoint areas eventually spread to produce a homogenous area seen on the latest follow-up (Fig. 4, top right). Another fluorescein angiogram done 17 months later showed that the atrophic macular lesions had enlarged in both eyes and more focal areas of hyperfluorescence had developed in the extramacular region (Fig. 4, bottom right).

Case 5—A 27-year-old white man with fundus flavimaculatus demonstrated bilateral complete ring scotomata dense to 18-mm white targets at a testing distance of 1 m. Visual acuity was 20/20 in each eye. Two years later, an increase in the density of the ring scotomata was demonstrated. This was followed by loss of central vision several years later.

The family history revealed that symptoms suggestive of ring scotomata and decreased visual acuity had developed in a sister in her fourth decade, and a disturbance of central vision had developed in a paternal male first cousin. We did not examine either person.

Case 6—A 56-year-old white man with fundus flavimaculatus had bilateral complete ring scotomata dense to a 35-mm white target at 1-m testing distance. Visual acuity was R.E.: 20/20, and L.E.: 20/30+. Mild pigment derangement was visible in the macular region of the left eye.

Discussion

Fundus flavimaculatus must be differentiated from the numerous conditions causing a "flecked retina" appearance with or without macular[3-6] changes. The diagnosis generally

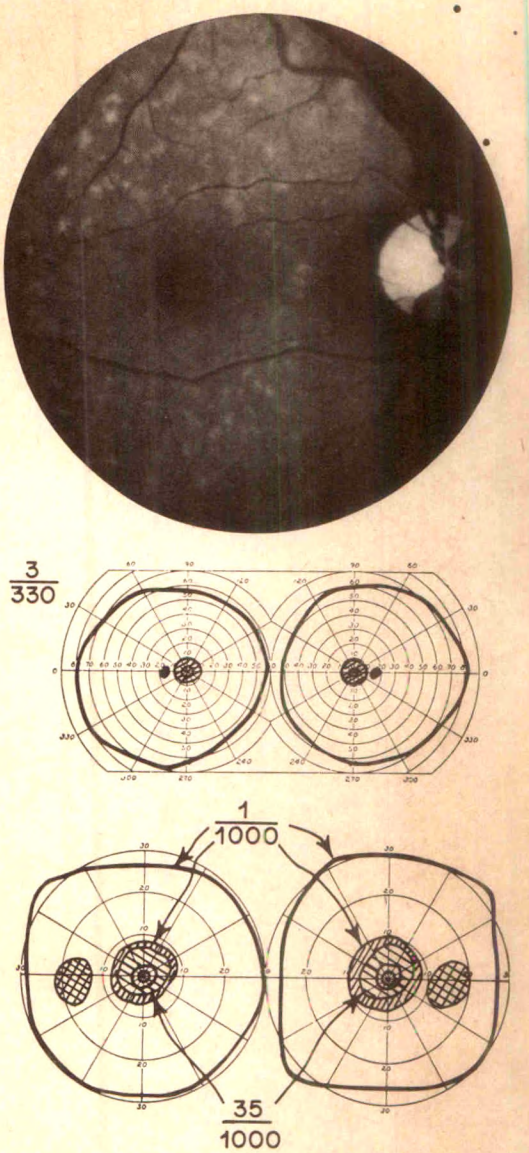


Fig. 3 (Passmore and Robertson). Top, Right eye. Bottom, Visual fields show bilateral ring scotomata dense to 35/1,000 white target. Visual acuity is 20/25 in both eyes.

can be made on recognizing the presence of unevenly distributed yellowish irregular fleck-like lesions at the posterior pole. The typical lesion appears to lie at the level of the deep retina or pigment epithelium.[2] Newly appearing lesions tend to develop peripherally to those already present. As a rule, the newer lesions have fairly distinct borders and tend to obscure background

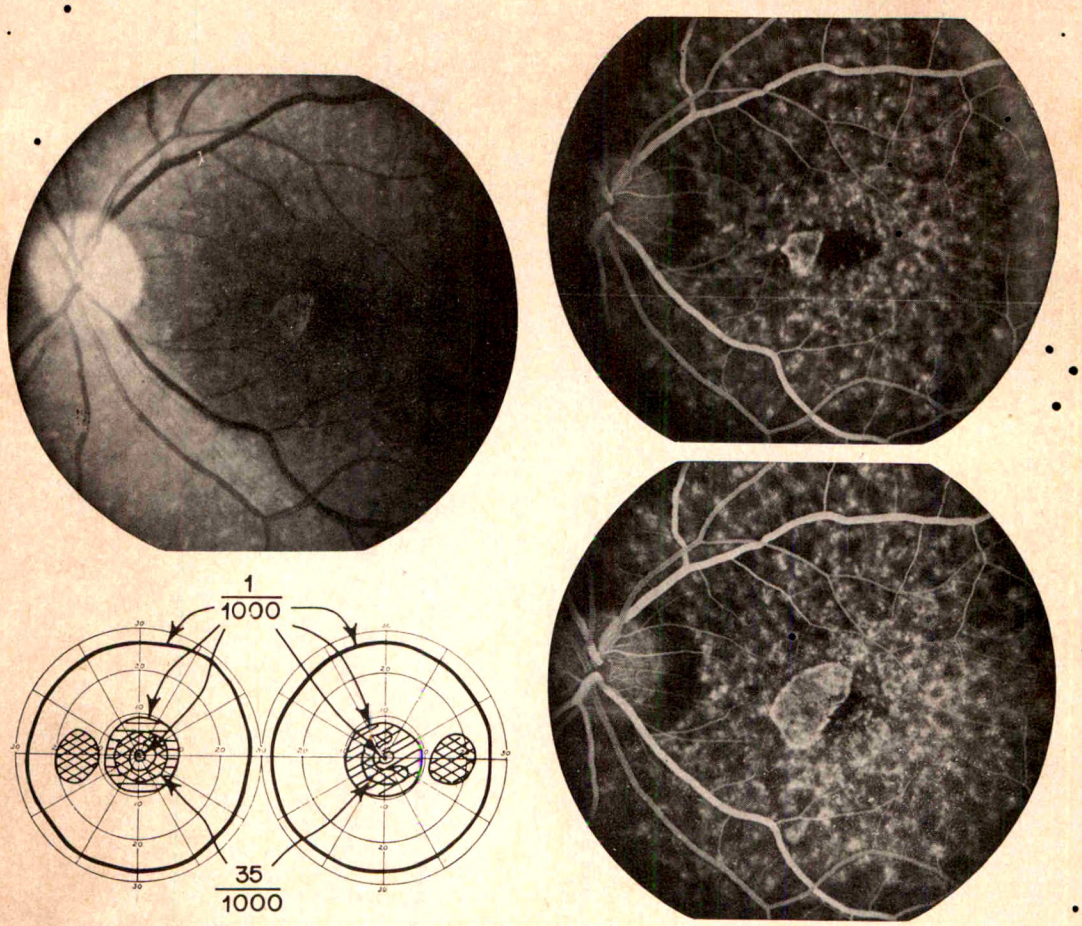


Fig. 4 (Passmore and Robertson). Top left, Left eye showing flecked pattern of fundus flavimaculatus. The solitary atrophic circumscribed paramacular lesion demonstrated a metallic sheen that seemed to originate at the level of the deep retina. Bottom left, Visual fields show complete ring scotoma dense to 1/1,000 white target in right eye and complete ring scotoma dense to 35/1,000 white target in left eye. Atrophic-appearing macular lesions, obvious clinically, were not distinctly associated with corresponding field defects. Visual acuity was R.E.: 20/20, and L.E.: 20/30. Top right, Fluorescein angiogram of left eye during venous phase (visual acuity, 20/30). Bottom right, Seventeen months later, there is a clear progression in size of the macular lesion (visual acuity, 20/300). Some hyperfluorescent areas were enlarged, whereas others seemed to have disappeared or become less obvious.

fluorescence during fluorescein angiography, whereas the older lesions tend to have faded indistinct boundaries and generally fluoresce during angiography. In some areas, their numbers may be sufficient to produce confluency.

In addition to the yellowish irregular flecks scattered about the posterior pole, there may be discrete atrophy of the pigment in the macular region. This seems to be present in 50% or more of the cases.[1,2] When there is recognizable atrophy of the pigment in the macular region, color vision may be impaired, and visual acuity is usually greatly reduced. At this stage, the retinal findings appear indistinguishable from advanced Stargardt's disease.[1,5,7] The advanced stages of Stargardt's disease and fundus flavimaculatus may appear identical, but it is probably incorrect to say that they are the same disease although this has been suggested by some authors.[5] Although Stargardt's disease may be associated with yellowish flecks in the posterior pole, the flecks appear after

the development of the atrophic changes in the macula. Conversely, fundus flavimaculatus may assume a relatively pure form without macular atrophy. Since Stargardt's original descriptions[7] indicated that macular changes preceded the development of the irregular flecks, it seems reasonable to accept Deutman's[7] suggestion to reserve the term fundus flavimaculatus for the condition in which macular changes appear only after the development of the yellowish flecks and also for the purer condition where the yellowish flecks are seen without macular atrophy.

Macular changes may have developed before the flecked lesions in some of our patients; nevertheless, the appearance of the fundi at the time we first examined the patients was compatible with the diagnosis of fundus flavimaculatus in five patients (Cases 1, 3-6).* We included Case 2 in this report because it represents an altered expression of fundus flavimaculatus, inasmuch as a sibling exhibited discrete lesions characteristic of fundus flavimaculatus.

The finding of ring scotomata in these patients appears to be newly recognized. The relatively good visual acuity in these six patients in the face of dense ring defects surrounding fixation indicates that these are true ring scotomata rather than central scotomata that have been spuriously recorded as ring defects because of poor fixation. Harrington[8] defined a ring scotoma as an irregular or partially circular visual field defect that surrounds the fixation point at varying distances with more or less completeness, having a shape not conforming to any nerve fiber pattern. As such, Walsh and Hoyt[9] listed ring scotomata as occurring in association with retinal bleaching by diffuse light, increased refractive errors, chorioretinitis, optic nerve lesions, migraine, malnutrition, hysteria, and retinitis pigmentosa. Stoll[10] described ring scotomata in cases of trauma to the head or eye and in central serous retinopathy. In addition, Duke-Elder[11] listed gyrate atrophy of the choroid and central choroidal sclerosis. Krill[3] added the hereditary cone degenerations. Chloroquine[12] and sparsomycin[13] toxicity may also cause ring scotomata.

In 1965, Carr[14] reported five cases of fundus flavimaculatus, among which was one patient with paracentral scotomata and another with centrocecal scotoma. He did not mention complete ring scotomata in any of his cases. Klien and Krill[2] mentioned paracentral scotomata in six cases with little or no impairment of acuity. Krill[3] described a transient stage in the evolution of fundus flavimaculatus in which there was a bull's eye appearance seen ophthalmoscopically that could be demonstrated further by fluorescein angiography. Ring scotomata might be expected with such lesions, although Krill did not define them in any of his cases. Weise and Yannuzzi[15] recently described the cases of nine patients with ring maculopathy observed on routine ophthalmoscopic examination and on fluorescein angiography, among which was one case of suspected Stargardt's disease and one case of fundus flavimaculatus. Although visual field defects were not described, ring scotomata might well have been present had tests been carried out to detect them. Deutman[16] recently described four cases of a new entity that he called "benign concentric annular macular dystrophy," in which central scotomata are associated with ring-like parafoveal depigmentation. The condition is dominantly inherited and clearly distinct from fundus flavimaculatus; fluorescein angiography in these cases demonstrated multiple small hyperfluorescent paramacular transmission defects. Although these findings suggest that ring scotomata might be present, they were not recognized in any of Deutman's

* We observed a 30-year-old man, with what we considered to be Stargardt's disease, who had developed yellowish flecks in the posterior pole and ring scotomata dense to 35-mm white targets at 1-m testing distance. Visual disturbances first occurred when he was 19 years of age and visual acuity was 20/25 or better until age 34, when visual acuity in one eye was 20/200, two years after demonstration of the ring defects.

cases. In one of our cases, fluorescein angiography demonstrated a ring maculopathy that led us to predict ring scotoma. In at least two of our cases, however, the presence of ring defects could not be anticipated on the basis of fluorescein angiography.

The presence of ring scotomata associated with fundus flavimaculatus in our six patients was surprising since, to the best of our knowledge, this had not been reported by others who had recorded visual fields in this disease. Though the ring defect is not an invariable finding, it was demonstrated in six of the 11 cases we have studied adequately. The finding of ring scotomata in some cases may aid in the diagnosis of fundus flavimaculatus; but perhaps more importantly, it may help explain visual complaints that seem out of proportion to measured central visual acuity. Also, the demonstration of ring scotomata places the condition with other diseases known to affect the rod-cone or pigment-epithelial layers or both, in which ring scotomata occur. Like many other toxic, dystrophic, and degenerative conditions that cause ring scotomata, in fundus flavimaculatus there is yet no reliable explanation for the particular susceptibility of the perimacular pigment epithelial-outer retinal complex to early selective loss of function.

To date, evidence suggests that the presence of ring scotoma is an ominous finding even when associated with normal visual acuity: in three of our patients this finding has been followed by the loss of central vision within 1½ to four years. Moreover, in one other patient, ring scotomata have increased during 3½ years, although without appreciable change in visual acuity.

Summary

Ring scotomata were associated with fundus flavimaculatus in six patients. The demonstration of ring scotomata in patients with fundus flavimaculatus helps to explain persistent visual complaints that may exist in the presence of normal central visual acuity. In many instances, ring scotomata cannot be predicted on the basis of the ophthalmoscopic findings. The presence of ring scotomata appears to be an ominous finding, even when associated with normal central visual acuity, for in three of our patients, it preceded loss of central vision by 1½ to four years.

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CLINICAL-PATHOLOGICAL CORRELATION IN MASSIVE PERIRETINAL PROLIFERATION

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After retinal detachment has been produced in the owl monkey, some eyes develop a clinical picture that is similar to what has been called massive vitreous retraction (MVR) or massive preretinal retraction (MPR) in humans. Histologic studies of these eyes show that vitreous strand formation and fixed folding of the retina, which are diagnostic of this condition, are caused by cellular membranes that are formed by metaplastic pigment epithelial cells[1] and glial cells.[2] To stress the importance and ubiquity of these proliferating cells in the posterior part of the eye, we suggest that this condition be called massive periretinal proliferation (MPP).

We give a detailed description of the clinical picture observed in this disease, and correlate it with pathological findings. Ophthalmoscopically, there are a great variety of lesions caused by the same proliferative process. Fixed folding of the retina is part of this periretinal proliferative process and is caused by membranes consisting of pigment epithelial cells or glial cells. An exaggerated end stage of massive periretinal proliferation in owl monkeys is similar to what has been called massive vitreous retraction or massive preretinal retraction in humans.

MATERIALS AND METHODS

Retinal detachments were produced in 45 owl monkey eyes by a method previously described.[3] The detachment was total in most of the cases after two to three weeks. The eyes were examined at least twice weekly by indirect ophthalmoscopy and fundus contact lens. Fundus photographs were taken. Eyes were enucleated after four weeks (11 eyes), nine weeks (25 eyes), ten weeks (one eye), 12 weeks (one eye) 16 weeks (three eyes), five months (two eyes), and six months (two eyes). Immediately before enucleation 0.2 ml of 6% phosphate-buffered glutaraldehyde was injected through the pars plana into the vitreous cavity to preserve the shape of the globe and to hasten fixation. The eyes were then enucleated, immersed in glutaraldehyde, and immediately opened circumferentially anterior to the ora serrata. Areas of interest, always at some distance from the retinal hole, were photographed at high magnification under the dissecting microscope while the eye remained immersed in the fixative. Preparation techniques for light and electron microscopy have been described in a previous paper.[2]

RESULTS

We present the clinical-pathological description in the sequence that an ophthalmologist usually examines the posterior eye: first, intravitreal lesions, then preretinal lesions, and finally subretinal lesions. To facilitate better understanding of the development and dynamics of the underlying pathologic process, we describe small and simple lesions first, followed by larger and more complicated ones. The cells involved in this periretinal process were identified as metaplastic pigment epithelial cells[1] and glial cells.[2]

Three morphologically different types of metaplastic pigment epithelial cells were found: (1) round, single pigment epithelial macrophages; (2) spindle-shaped, mostly

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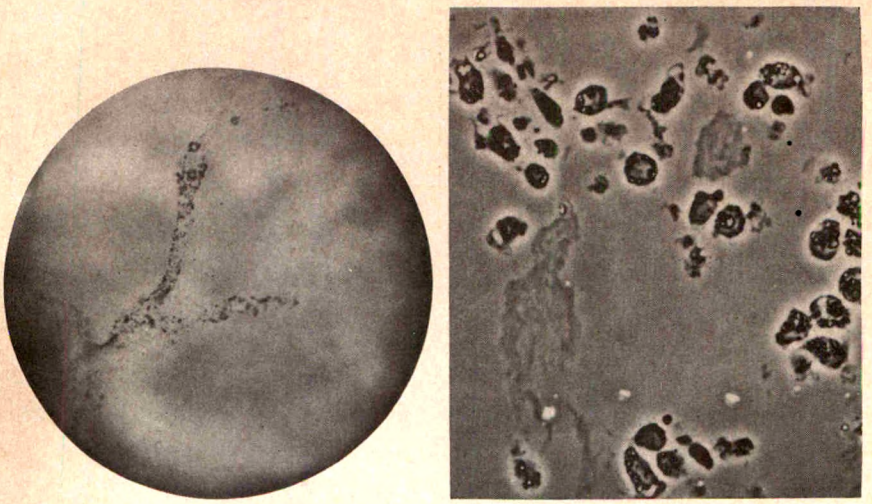


Fig. 1 (Laqua and Machemer). Left, Intravitreal pigmented dots and clumps (×40). Right, These are pigment epithelial macrophages that have settled down on vitreous structures; four-week-old detachment (phase contrast, ×250).

unpigmented, fibrocyte-like, pigment epithelial cells; (3) highly differentiated pigment epithelial cells similar to those found on Bruch's membrane.

A single type of glial cell was found. These glial cells were spindle-shaped and unpigmented and grew out of the retina through a focal interruption in the internal or external limiting membrane. Typically glial membranes remained connected to the retina by a thin bridge of tissue.

Intravitreal proliferation — Intravitreal proliferation exclusively consisted of metaplastic pigment epithelial cells.

Clinically, single brown pigmented dots and clumps were found on the vitreous body mainly in the lower half of the eye but also floating freely in the vitreous cavity and on

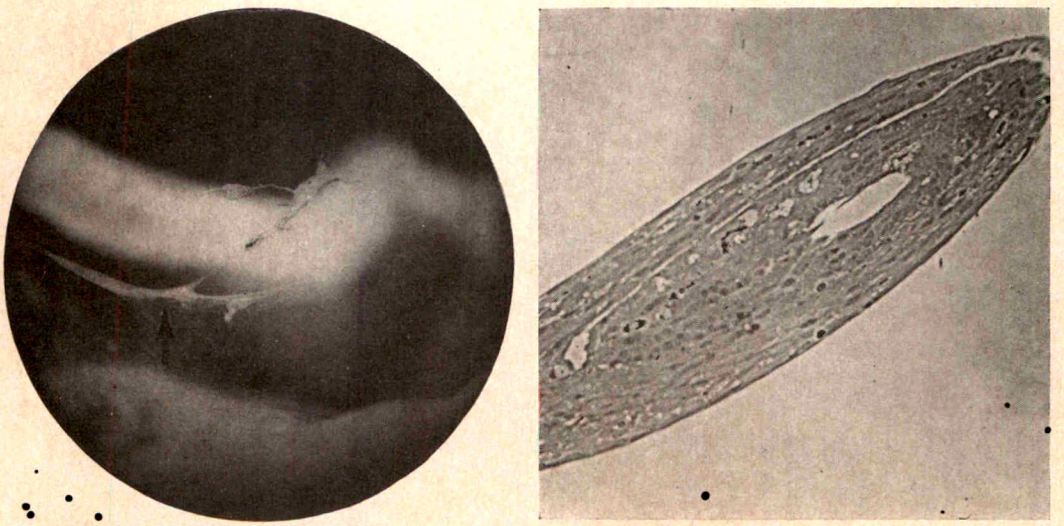


Fig. 2 (Laqua and Machemer). Left, Stiff semitransparent vitreous strands (arrow) (×20). Right, They consist of fibrocyte-like pigment epithelial cells growing along a vitreous scaffold; 16-week-old detachment (phase contrast, ×160).

the posterior surface of the lens. Histologically, these structures were single, round, heavily pigmented, pigment epithelial macrophages (Fig. 1). They were identical to what in human retinal detachment has been described as "tobacco dust" and is thought to be pathognomonic for a retinal break.[4]

In some eyes, in addition to an increasing pigmentation, there were changes of vitreous structures. Semitransparent vitreous strands and membranes formed. They looked firm and did not float freely with eye movements. Histology of these strands and membranes revealed spindle-shaped, sparsely pigmented cells that were proliferating along a collagenous vitreous scaffold. These cells were metaplastic pigment epithelial cells of the fibrocyte-like type (Fig. 2). Semitransparent and immobile vitreous strands and membranes occasionally attached to the retina causing fixed retinal folds. Two different types of fixed folds were seen: a circumferential fold and localized, irregular folds.

In a circumferential fold, a vitreous membrane in the anterior vitreous cavity had several round to oval openings. This membrane was circumferentially attached to the vitreous base and peripheral retina. It was semitransparent and occasionally was covered by pigmented dots and clumps. The membrane was stiff and did not change position with eye movements. The retina was highly detached and fixed bullae, which did not change their appearance with eye movements, were pulled centrally by the membrane. Histology showed condensed vitreous covered on both sides by the three types of metaplastic pigment epithelial cells; single or clumped pigment epithelial macrophages, fibrocyte-like, and highly differentiated pigment epithelial cells (Fig. 3).

In irregular folds, localized vitreous membranes were found in the posterior vitreous cavity. Typically, the membrane was attached in some areas to the retina, had a slightly reduced transparency, and contained pigmented dots and clumps. Usually it was associated only with small areas of retinal

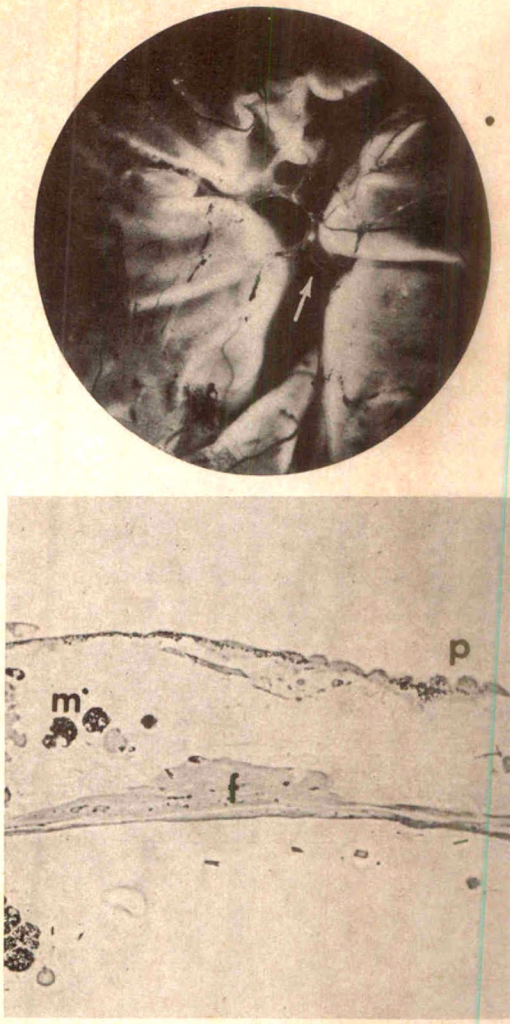


Fig. 3 (Laqua and Machemer). Top, Circumferential fold caused by a vitreous membrane (arrow) circumferentially attached to the vitreous base and peripheral retina (×10). Bottom, The membrane is composed of condensed vitreous fluid, covered on both sides by metaplastic pigment epithelial cells. Pigment epithelial macrophages (m), fibrocyte-like pigment epithelial cells (f), and highly differentiated pigment epithelial cells (p); six-month-old detachment (phase contrast, ×160).

folding, bridging the valleys between the folds. The folds had sharp, irregular contours and did not change with eye movements. Histologically the membrane was composed of condensed vitreous, single or clustered pigment epithelial macrophages, and strand-forming, fibrocyte-like pigment epithelial cells (Fig. 4).

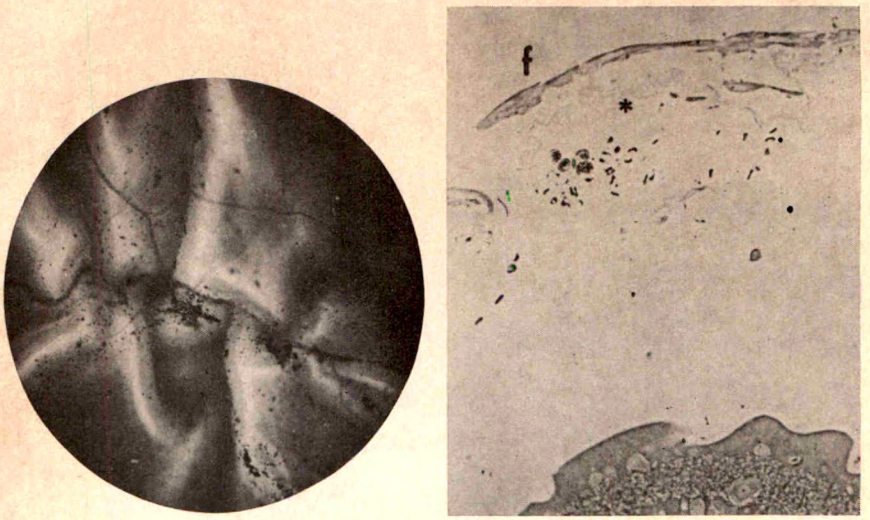


Fig. 4 (Laqua and Machemer). Left, Localized irregular fold (×40). Right, Vitreous membrane is composed of condensed vitreous (asterisk), strand-forming, fibrocyte-like pigment epithelial cells (f) and pigment epithelial macrophages and blood cells; nine-week-old detachment (phase contrast, ×160).

Preretinal proliferation—Preretinal proliferations consisted of metaplastic pigment epithelial or glial cells, or both.

Pigmented dots or clumps were irregularly distributed on the inner retinal surface, particularly inferiorly. Sometimes they seemed to follow the course of the vessels or were arranged in parallel lines corresponding to a fine wrinkling of the internal limiting membrane. Histologically they were pigment epithelial macrophages identical to those found in the vitreous. Pigment epithelial macrophages themselves never affected the underlying retina but since they occasionally settled down in the valleys between fine, superficial, retinal folds, they indicated areas of retinal folding caused by a preretinal membrane (Fig. 5).

Preretinal membranes nearly always affected the underlying retina, causing it to fold. Four types of fixed folds were seen: superficial and full-thickness starfolds, and superficial and full-thickness irregular folds.

A superficial starfold, a discrete lesion, consisted of a small, round center from which fine, superficial wrinkles of the retina

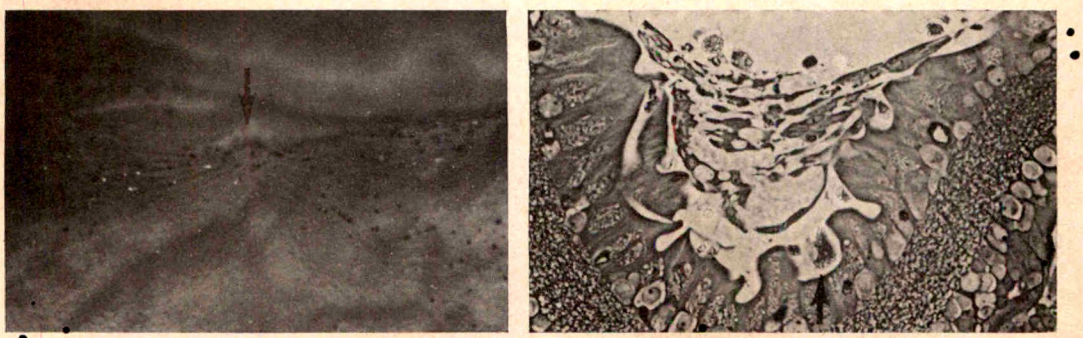


Fig. 5 (Laqua and Machemer). Left, Superficial starfold with round and slightly pigmented center (arrow) (×40). Right, The center consists of fibrocyte-like pigment epithelial cells. Collagenous material is deposited between the cells. Single pigment epithelial macrophages are in the valleys (arrow); nine-week-old detachment (phase contrast, ×250).

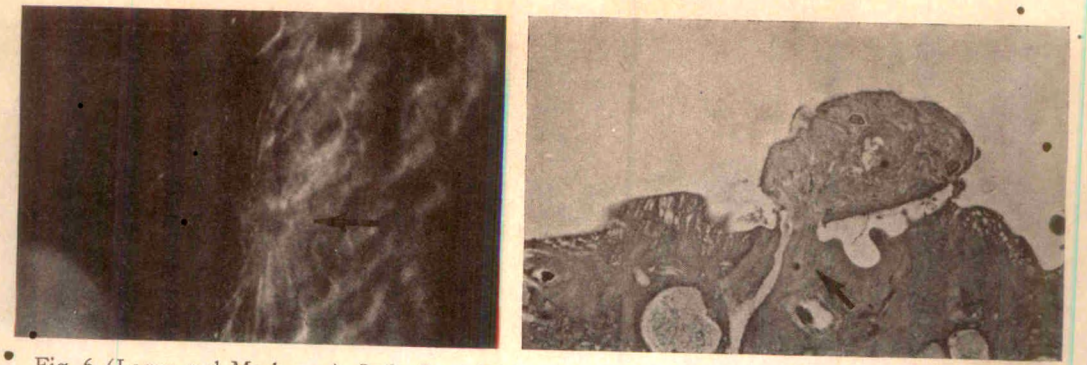


Fig. 6 (Laqua and Machemer). Left, Superficial starfold with an unpigmented center (arrow) (×40). Right, This center consists of a clump of preretinal glial cells connected to the retina by a bridge of tissue. A retinal cell (arrow) apparently is migrating out of the retina; nine-week-old detachment (phase contrast, ×400).

extended in a star-like manner over a considerable distance. The center appeared slightly elevated and slightly pigmented. The radiating folds were often lined with pigmented dots. Histologically, metaplastic, fibrocyte-like pigment epithelial cells were in the center, directly overlying the internal limiting membrane and folding the superficial layers. Collagenous material was deposited between the cells. Additional single pigment epithelial macrophages were detected in the valleys of the wrinkled retina (Fig. 5).

A second type of superficial starfold was similar to the one just described except that it was usually unpigmented. The main difference, however, was found histologically. The center had a small clump of cells directly connected to the retina by a thin bridge of tissue. These cells were glial cells that had grown out of the retina through a focal interruption in the internal limiting membrane. The superficial layers of the retina were folded. In the wrinkles of the internal limiting membrane there were no preretinal cells or remnants of the posterior cor-

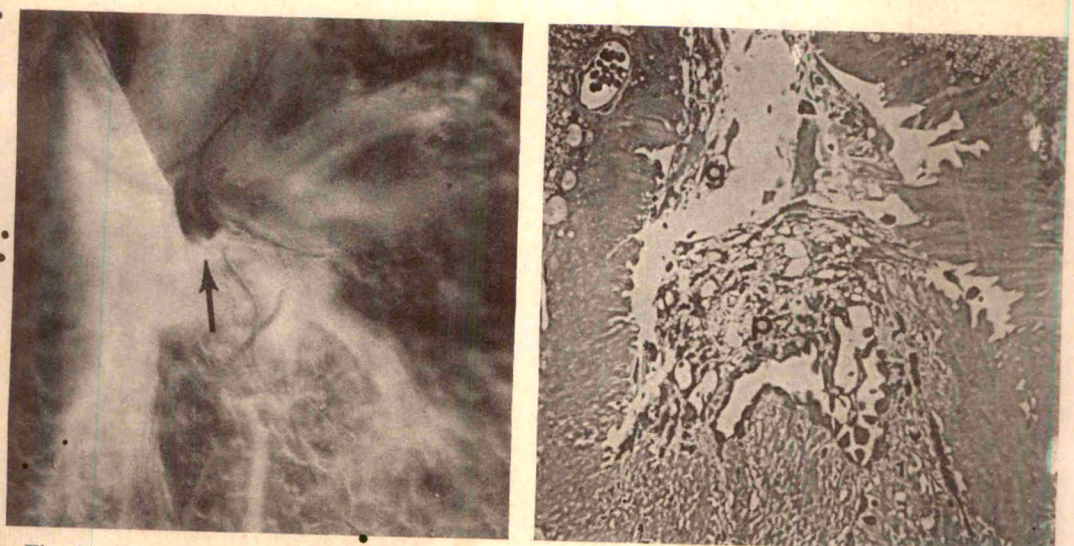


Fig. 7 (Laqua and Machemer). Left, Full-thickness starfolds with a depressed center (arrow) and converging folds that stop just before the center. There is a preretinal, slightly pigmented tissue (×40). Right, Tissue consists of metaplastic pigment epithelial cells (p) and glial cells (g); nine-week-old detachment (phase contrast, ×250).

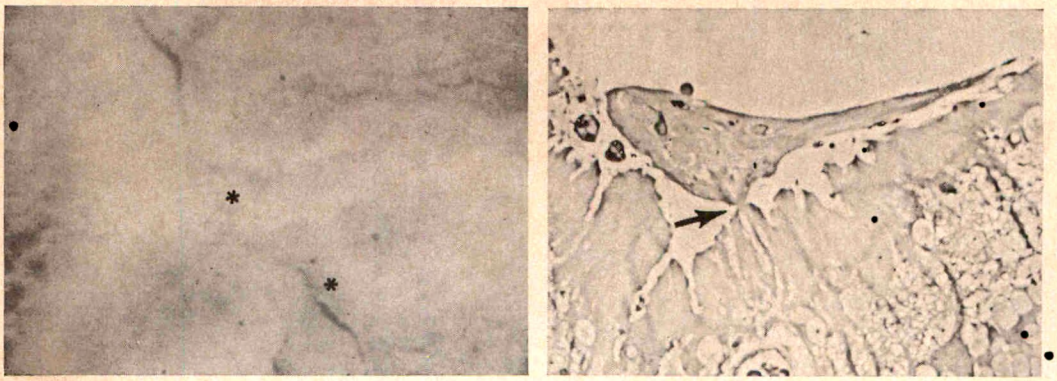


Fig. 8 (Laqua and Machemer). Left, Irregular, superficial folding of the retina with kinking of vessels and their disappearance for a short distance (asterisks) are indirect signs of a preretinal membrane (×40). Right, Preretinal glial membrane connected to the retina by a bridge of tissue (arrow). The membrane has folded the superficial layers of the retina and begins full-thickness folding; nine-week-old detachment (phase contrast, ×250).

tical vitreous cavity (Fig. 6). Superficial starfolds of glial origin were clinically similar to what has been described in humans as cellophane maculopathy[5] or surface wrinkling retinopathy[6] thought to be an early stage of macular pucker. Superficial starfolds are easily overlooked clinically, especially when they are located in the periphery. Clear media, optimal illumination, and examination with the contact lens at high magnification were needed to find them.

A full-thickness starfold was much easier to recognize. Typically, the retinal folds converged but terminated centrally without touching. The center of the starfold was depressed and preretinal tissue which sometimes is pigmented was recognized. Histologically, the central area delineated by the converging retinal folds was filled with tissue that consisted of metaplastic pigment epithelial cells as well as of glial cells. In addition to the clinically visible full-thickness folding,

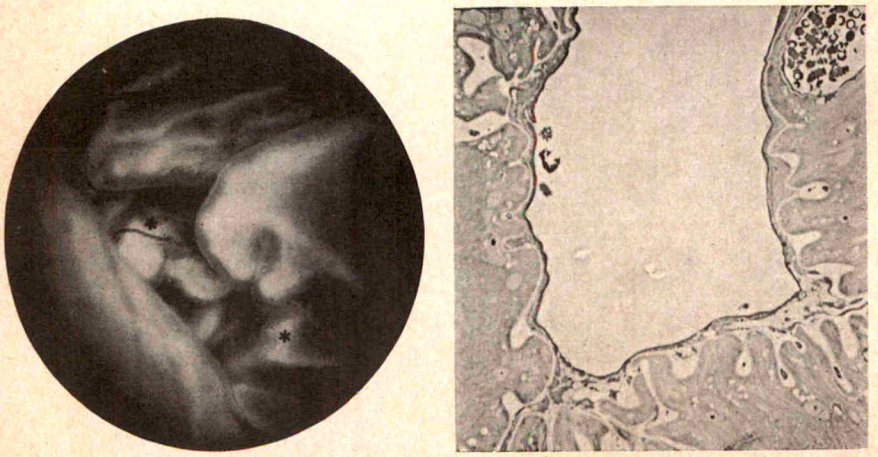


Fig. 9 (Laqua and Machemer). Left, Irregular, full-thickness folds with tortuous and kinked vessels and spotty pigmentation (asterisks) are signs of a preretinal membrane (×30). Right, Preretinal membrane consists of fibrocyte-like pigment epithelial cells with collagenous material deposited between the membrane and the folded retina. Note the prominent folding of superficial retinal layers in addition to the full-thickness folding; sixteen-week-old detachment (phase contrast, ×160).

there was extensive folding of the superficial retina as well (Fig. 7).

When a preretinal membrane was not localized, as in starfolds, but extended over a large area, it caused larger areas of the retina to fold, leading to the picture of superficial or full-thickness irregular folds. The membrane usually was transparent and therefore difficult to visualize. There were indirect signs, however, that indicated the presence of a preretinal membrane. First, irregular, glistening reflexes and fine wrinkles of the superficial retina occurred. Second, vessels appeared kinked and tortuous. Third, vessels seemed to disappear for short distances. Fourth, details typical for detached retina such as minute cystoid changes became undetectable. Fifth, in addition to irregular wrinkles of the superficial layers, the full-thickness of the retina was occasionally folded. If we saw no pigmentation, histology demonstrated a preretinal membrane most likely consisting of glial cells and connected to the retina by a bridge of tissue (Fig. 8). If the retina was spottily pigmented but otherwise similar to the one just described, spindle-shaped, sparsely pigmented, or unpigmented cells were found; the so-called fibrocyte-like pigment epithelial cells. A layer of collagenous material was deposited between these cells and the heavily folded retina (Fig. 9).

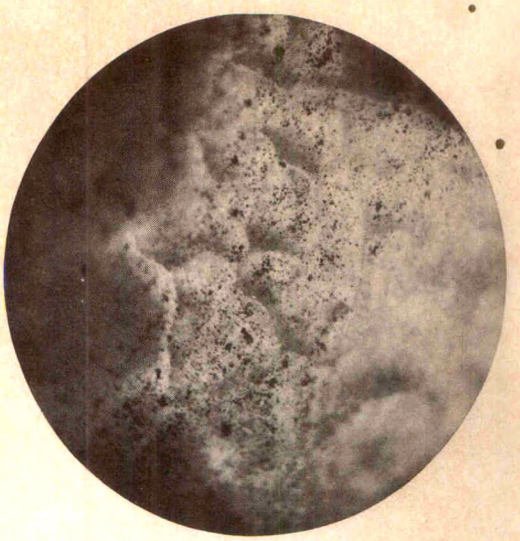


Fig. 10 (Laqua and Machemer). Outer retinal surface with multiple, pigment dots consisting of pigment epithelial macrophages identical to those found intravitreally and preretinally; nine-week-old detachment (×40).

Subretinal proliferations—Subretinal proliferations consisted of pigment epithelial cells or glial cells, or both. Multiple minute pigmented dots and clumps lying directly on the posterior surface of the retina were usually undetectable unless the retina folded

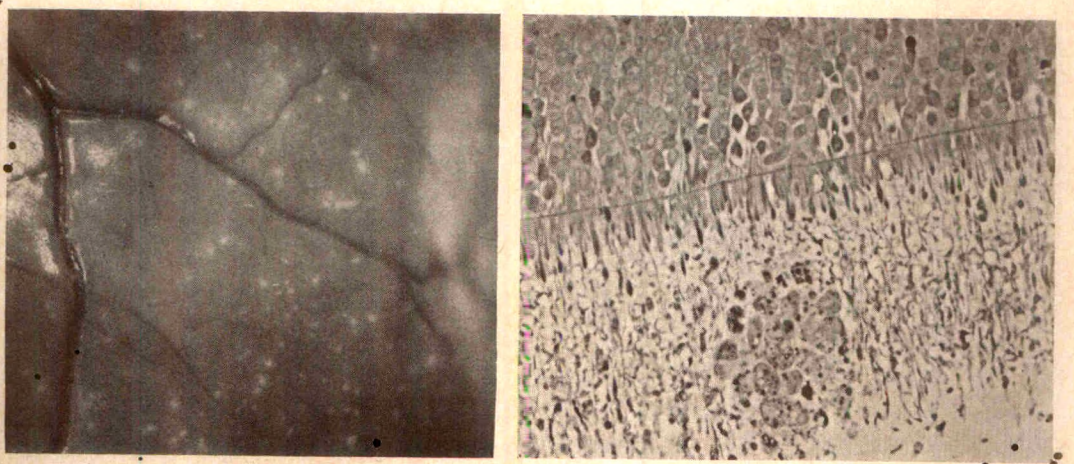


Fig. 11 (Laqua and Machemer). Left, White retroretinal dots visible through the retina (×25). Right, Dots consist of clusters of pigment epithelial macrophages between outer segments; four-week-old detachment (phase contrast, ×250).

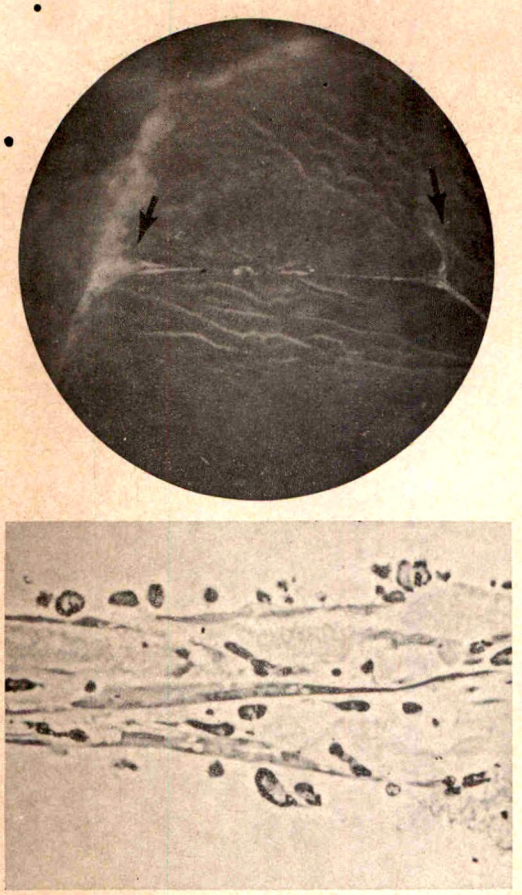


Fig. 12 (Laqua and Machemer). Top, A spottily pigmented subretinal strand is seen by direct inspection of the outer retinal surface. At each end (arrows), it is firmly connected to the outer retinal surface (×25). Bottom, The strand consists of spindle-shaped glial cells and fibrin. Round pigment epithelial macrophages account for the clinically visible pigmentation; four-week-old detachment (phase contrast, ×160).

over as in the case of a giant tear. Histologically, they were pigment epithelial macrophages identical to those found intravitreally and preretinally (Fig. 10).

Retroretinal white dots that are common in retinal detachment were visible through the retina. They were irregularly distributed and more prominent in the inferior half of the fundus. Histologically, they comprised clusters of sparsely pigmented cells that showed active proliferation. These cells originated from pigment epithelial macrophages that had lost most of their pigment through continuous multiplication[1] (Fig. 11).

Clinically the most impressive retroretinal changes were the yellow-white subretinal strands that have been described since the early days of ophthalmology.[7] These branching, straight, or slightly curved, subretinal structures often formed a network with multiple interconnections. Ophthalmoscopically,

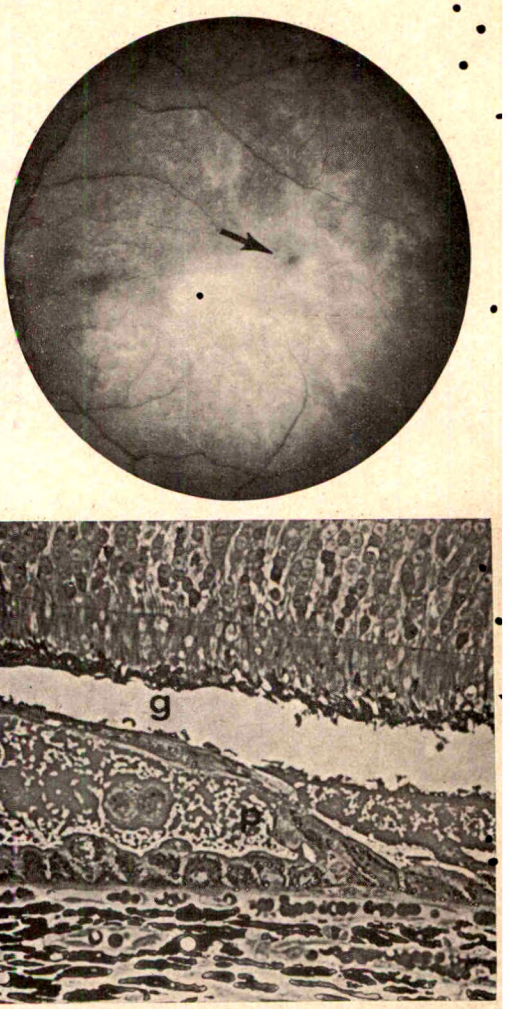


Fig. 13 (Laqua and Machemer). Top, An extensive subretinal membrane appears unpigmented except for a small spot-like area (arrow) (×20). Bottom, Histology demonstrates a subretinal glial membrane. Where the membrane touches the pigment epithelial layer, proliferating pigment epithelial cells (p) connect to the glial membrane (g) and account for the clinically visible pigmentation; 21-week-old detachment (phase contrast, ×400).

subretinal strands appeared to be deep to the retina. Direct inspection of the outer retina after enucleation showed that they lay close to the outer surface of the retina and that they were firmly connected to the retina at each end (Fig. 12).

Closely related to subretinal strands were the subretinal membranes that ophthalmoscopically also lay deep to the retina and had the same yellowish appearance. They had scalloped borders and short finger-like projections that sometimes became continuous with the described subretinal strands. Subretinal strands and membranes occasionally showed spotty pigmentation. Pigmentation was especially pronounced in an area of a flat detachment when a strand or membrane touched the pigment epithelial layer (Fig. 13). Subretinal strands and membranes had the same histologic characteristics. They either lay directly on the photoreceptor layer or extended into the subretinal space. They did not affect the overlying retina since cellular connections to the retina are not frequent. The cells that built up the strands and membranes were arranged in parallels, spindle-shaped, and unpigmented, and were identified as glial cells. They were mixed with an amorphous acellular material that was electron microscopically identical to fibrin.[2] The clinically visible pigmentation was related to pigment epithelial macrophages that occasionally settled down on the surface of the strands or membranes (Fig. 12). In areas of a flat detachment, where strands or membranes came into contact with the pigment epithelial layer, fibrocyte-like, pigment epithelial cells occasionally grew along this glial structure and also contributed to pigmentation of these strands and membranes (Fig. 13). Subretinal membranes consisting exclusively of metaplastic pigment epithelial cells were described histologically in a previous paper.[1] However, they are rare and were not found in this experiment.

Subretinal glial proliferations can cause fixed folding of the retina. The subretinal proliferation was then covered by the folded retina and was no longer visible. Two types of fixed folds developed; full-thickness starfolds and full-thickness irregular folds.

A full-thickness starfold with subretinal proliferation had an elevated center and the folds were connected to each other in that they crossed the center. The center occasionally appeared pigmented. Histologically, subretinal glial tissue with multiple cellular connections to the outer retina caused the retina to fold. The clinically visible pigmentation was mostly due to an intraretinal ac-

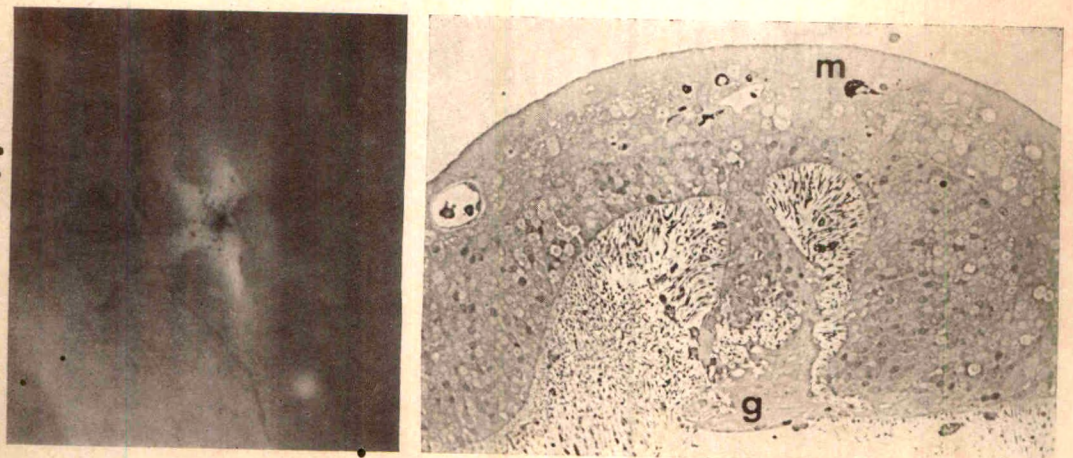


Fig. 14 (Laqua and Machemer). Left, Full-thickness starfold with an elevated pigmented center and radiating folds which centrally are connected to each other (×40). Right, Subretinal glial tissue (g) connected to the outer retina. Intraretinal pigment epithelial macrophages (m) account for the clinically visible pigmentation; nine-week-old detachment (phase contrast, ×160).

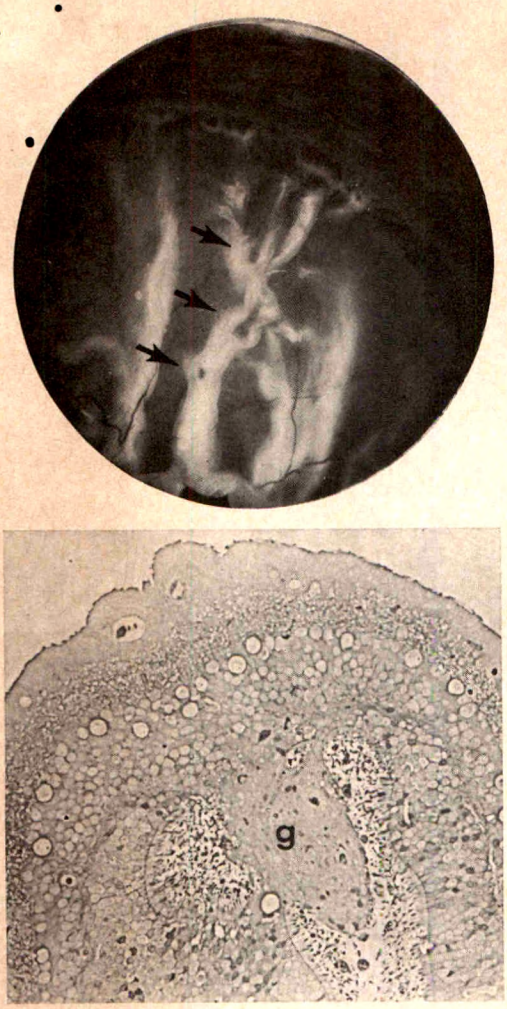


Fig. 15 (Laqua and Machemer). Top, Irregular folding of the retina with several pigmented knob-like areas (arrows) (×15). Bottom, These areas represent localized subretinal glial proliferations (g). Pigmentation is caused by sub- and intraretinal pigment epithelial macrophages; nine-week-old detachment (phase contrast, ×160).

cumulation of pigment epithelial macrophages (Fig. 14). Full-thickness starfolds caused by subretinal proliferation were clinically distinguished from full-thickness starfolds caused by preretinal proliferation. The latter had a depressed center and the folds did not show a central connection but stopped just before the center. The different folding pattern was caused by the different location of the proliferative process (compare Figures 7 and 14). These different folding patterns of starfolds were observed clinically in humans.[8,9]

There were many full-thickness irregular folds that clinically had slightly different features, depending on the extent and degree of the subretinal pathology.

A localized form of irregular folds consisted of steep, branching folds with multiple slightly pigmented, knob-like areas. Histologically, these areas had a subretinal glial proliferation identical to that described for

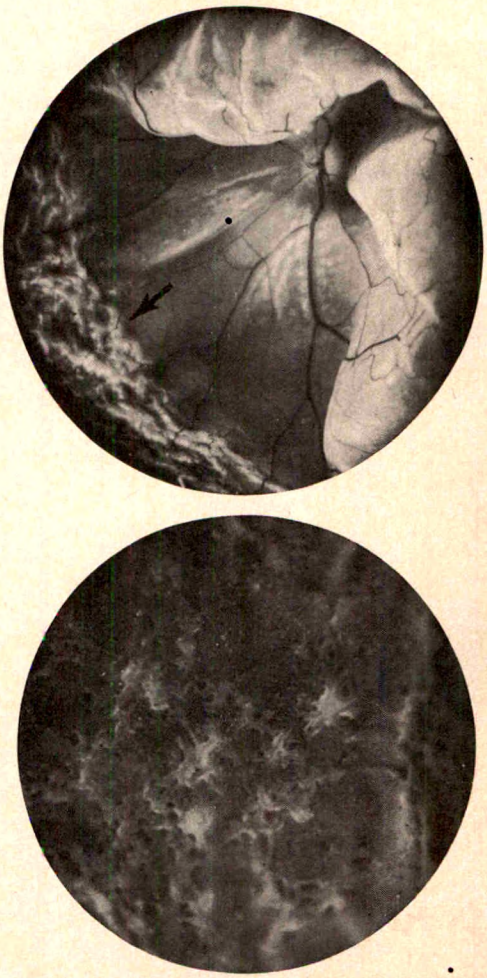


Fig. 16 (Laqua and Machemer). Top, Shallow, wave-like and confluent folds (arrow) (×10). Bottom, Direct inspection of the outer retinal surface after removal of sclera and choroid shows that in the area of folding, the outer retina is covered by multiple, small membranes; ten-week-old detachment (×15).

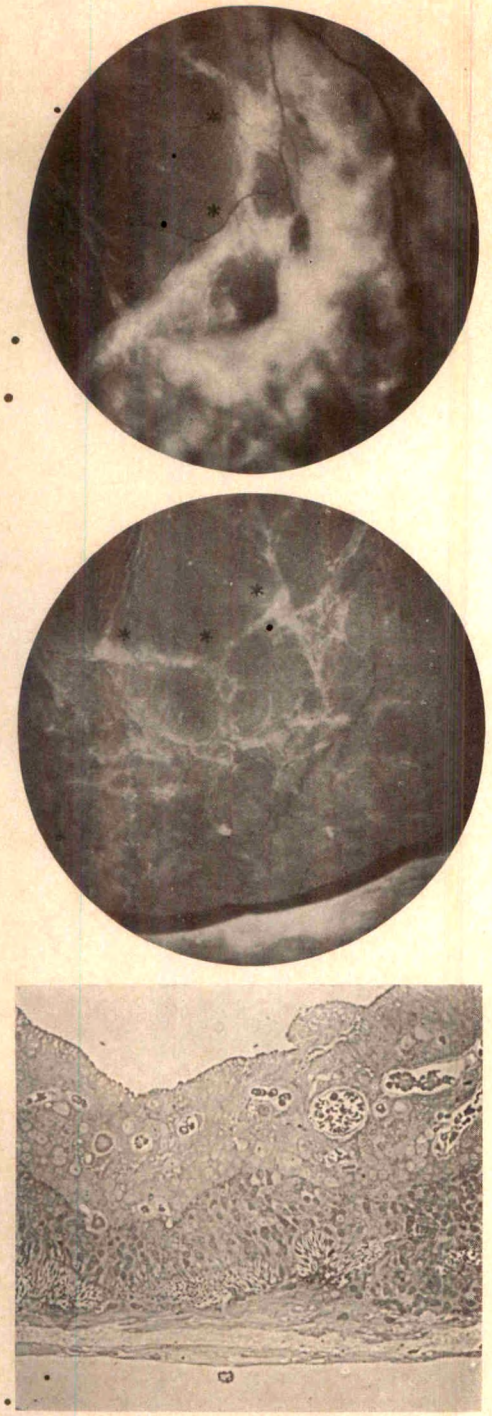


Fig. 17 (Laqua and Machemer). Top, Gross retinal folding with a superimposed fine, wave-like pattern (×20). Center, Outer retinal surface with a continuous membranous sheet covering an area corresponding to the folding. Asterisks indicate the border between normal detached retina and folded retina (×20). Bottom, Histology demonstrates a glial membrane with multiple connections to the retina. Fibrin is found between the layers of glial cells. Note that the membrane is straight but the overlying retina is folded; four-week-old detachment (phase contrast, ×160).

the full-thickness starfold (compare Figures 14 and 15). Yet, the glial proliferations were not connected to each other. Only the resulting retinal folds were interconnected. Where the retina folded, it had lost its transparency even in areas where no subretinal pathology was demonstrated.

Sometimes larger areas of the retina were irregularly folded. They showed a multitude of shallow, wave-like, and confluent folds that typically had a yellowish coloration. Within the area of folding, it was not clear if the yellowish coloration was caused by folding of the retina or by some subretinal material. However, where the lesions faded out into the unfolded detached retina, a distinct yellowish material with an irregular pattern was seen deep to the retina. By direct inspection of the outer retinal surface after the eye was enucleated, multiple small membranes were firmly attached to the outer retinal surface. They had scalloped borders and finger-like projections that connected the membranes to each other and formed one large plane of interconnected membranes in an area corresponding to the folding (Fig. 16). Histologically, the membranes consisted of glial cells.

A similar and related pattern of irregular folds was characterized by gross folding of the retina, often with a superimposed wave-like pattern. The retina appeared yellowish and thickened with a loss of transparency. Yellowish material seemed to be deposited beneath the retina. Direct inspection of the outer retinal surface demonstrated a membranous sheath of varying and sometimes considerable thickness that covered an area corresponding to the folding. Frequently, toward its outer limits, holes were found in this membrane. Histologically, a multilayered

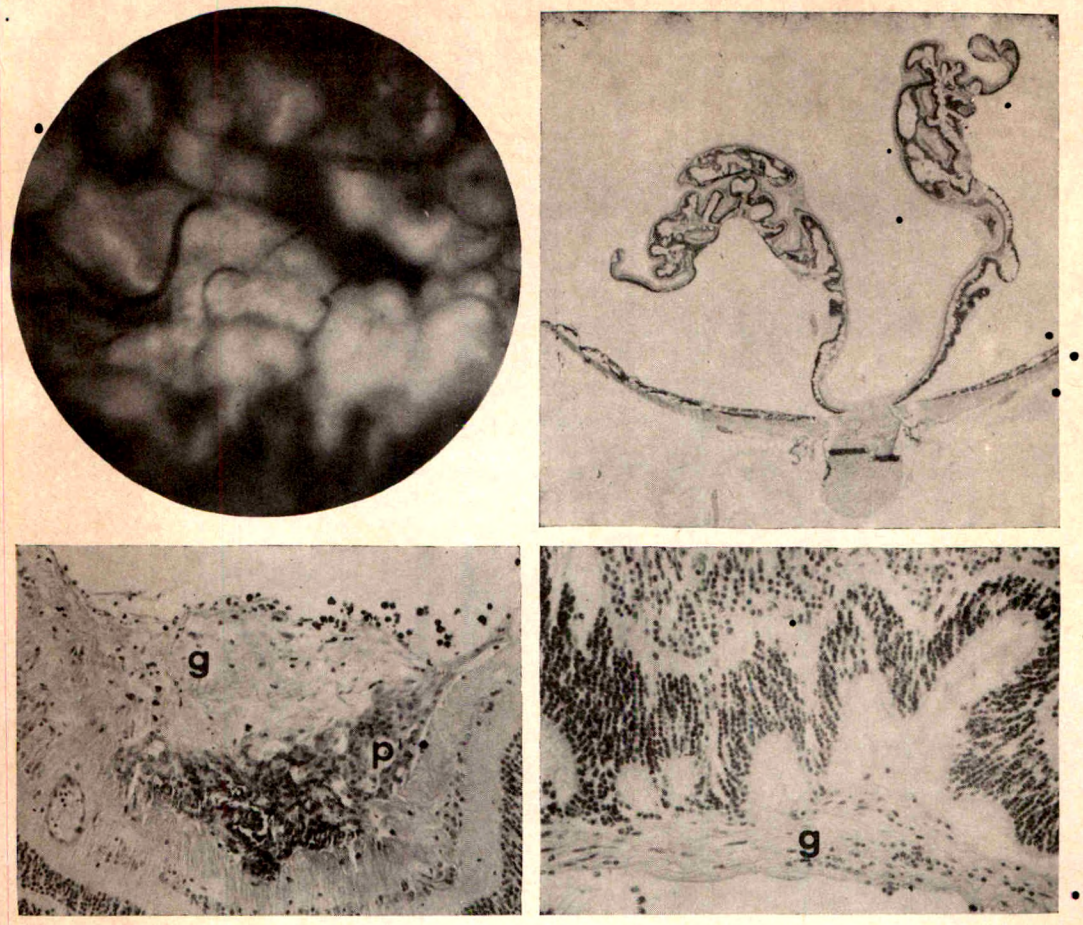


Fig. 18 (Laqua and Machemer). Top left, End-stage MPP with 360-degree dialysis. Top right, The heavily folded retina has shrunk toward the disk (PAS, ×3). Bottom left, Preretinally pigment epithelial cells (p) as well as glial cells (g) caused the retina to fold (PAS, ×100). Bottom right, Subretinally, glial membranes (g) are seen; 12-week-old detachment (PAS, ×160).

glial membrane had many connections to the outer layers of the retina. Fibrin and pigment epithelial macrophages were also present. This membrane pulled the retina into folds (Fig. 17).

End-stage MPP—For descriptive purposes, intravitreal, preretinal, and subretinal lesions were described separately. However, they usually occurred simultaneously and in various combinations. The resulting overall clinical picture is variable, depending on the type of lesions that combine with each other.

In a few eyes, extensive intravitreal, preretinal, and subretinal lesions combined to cause a characteristic clinical picture that we call end-stage MPP. The view of the fundus was usually hazy. The vitreous fluid was confined to the anterior vitreous cavity and occupied only part of its original volume. It was characterized by immobile and semitransparent vitreous strands and membranes and many pigmented dots or clumps that either floated freely or had settled down on the vitreous scaffold. The retina was highly detached and had a morning-glory appearance caused by a circumferential fold. This fold could be so extensive that the optic disk was not visible. The retina anterior to the circumferential fold often looked like normal detached retina. In the posterior part of

the funnel, however, multiple fixed folds occurred. The folds always involved the full-thickness of the retina and had a gross radial orientation with a superimposed irregular pattern. Additional starfolds occurred in some eyes. The retina was stiff and appeared thickened by a yellowish material beneath the retina. Preretinal membranes with variable pigmentation covered the inner retinal surface and obscured details of the retina.

In a case with a 360-degree dialysis, no circumferential retinal fold developed since tearing near the ora serrata separated the vitreal abnormalities from the retinal abnormalities. The vitreous remained anteriorly and the heavily folded retina shrank toward the optic nerve (Fig. 18).

In rare cases, we found a peculiar type of end-stage MPP that was clinically similar to the one we described. Multiple fixed folds occurred that had a gross radial orientation and a superimposed brain-like pattern. Histologically, however, the relevant pathological findings were confined exclusively to the outer surface of the retina. Extensive glial membranes covered the entire outer surface of the retina causing it to fold (Fig. 19).

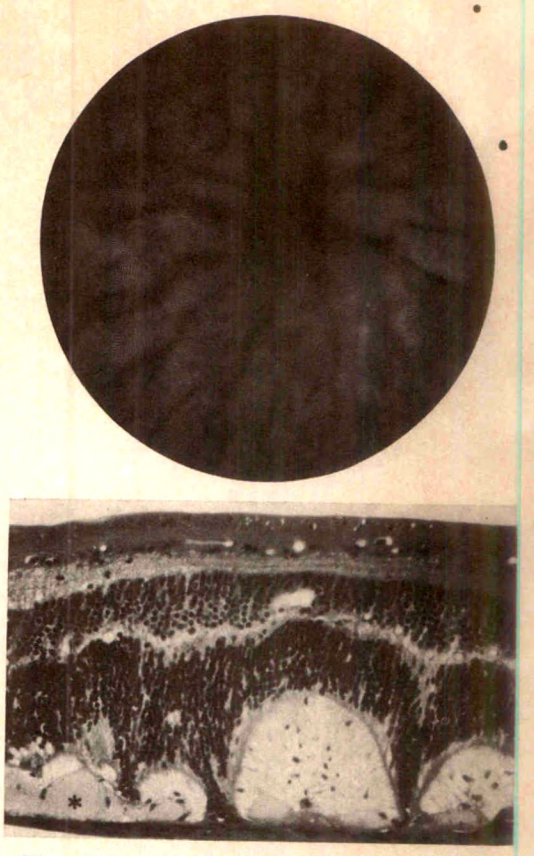


Fig. 19 (Laqua and Machemer). Top, Morning-glory detachment of the retina with fixed folds (PAS, ×10). Bottom, Histologically the whole outer surface of the retina is covered by a glial membrane. Fibrin is found internal to the membrane (asterisk); six-month-old detachment (PAS, ×60).

Discussion

Our previous histologic studies have shown that in experimental retinal detachment in the owl monkey, metaplastic pigment epithelial cells[1] and glial cells[2] proliferate along vitreous structures and on the inner and outer surfaces of the retina. We emphasize the ubiquity of cellular proliferation in the posterior part of the eye by calling this condition MPP. This clinical-pathological study shows that the MPP process encompasses a broad spectrum of lesions that have varying degrees and may occur in any combination with each other, causing a remarkable variability of the clinical picture.

In nearly all eyes with retinal detachment, pigmented dots and clumps (Figs. 1, 5, and 10) are found intravitreally, preretinally, and subretinally. These are cells that originate from the pigment epithelium.[1] The amount of intravitreal pigmented dots and clumps is indicative of the ongoing proliferative process and is a useful clinical factor for evaluating the degree and severity of MPP. When present, semitransparent, intravitreal strands and membranes (Fig. 2) may also serve as a valuable clinical sign of MPP. Retroretinal white dots (Fig. 11) and yellow subretinal strands and membranes (Figs. 12 and 13) are less frequent and, therefore, less helpful.

The most obvious and important clinical signs are fixed retinal folds. They are caused by the contraction of intravitreal, preretinal, or subretinal membranes. Whenever there is an adhesion between the mem-

TABLE

CLASSIFICATION OF FIXED FOLDS

	Cell Type	Type of Fixed Fold
Intravitreal membranes	Metaplastic pigment epithelial cells	Circumferential fold (Figs. 3 and 20, left) Irregular fold (Figs. 4 and 20, right)
Preretinal membranes	Metaplastic pigment epithelial cells or glial cells, or both	Superficial starfold (Figs. 5, 6, and 21, A) Full-thickness starfold (Figs. 7 and 21, C) Superficial irregular fold (Figs. 8 and 21, B) Full-thickness irregular fold (Figs. 9 and 21, D)
Subretinal membranes	Glial cells (?Pigment epithelial cells)	Full-thickness starfold (Figs. 14 and 22, left) Full-thickness irregular fold (Figs. 15, 16, 17, and 22, right)

brane and the retina, contraction forces of the membrane may be transmitted to the retina, thus causing it to fold. These folds are stiff and do not change their pattern with eye movements; thus the term fixed folds. There are several types of fixed folds that are distinguished from each other by their different folding patterns. Their pathogenic development is easily explained by examining the location, size, and strength of the membrane. We put the different types of fixed folds into some order (Table) and explained the proposed mechanism of their development (Figs. 20-22).

In the owl monkey eye, intravitreal, preretinal, and subretinal membrane formations may occur simultaneously and may be extensive, resulting in a clinical picture that we call end-stage MPP (Figs. 18 and 19). In its clinical aspect, it is identical to what has been called massive vitreous retraction or massive preretinal retraction in the human

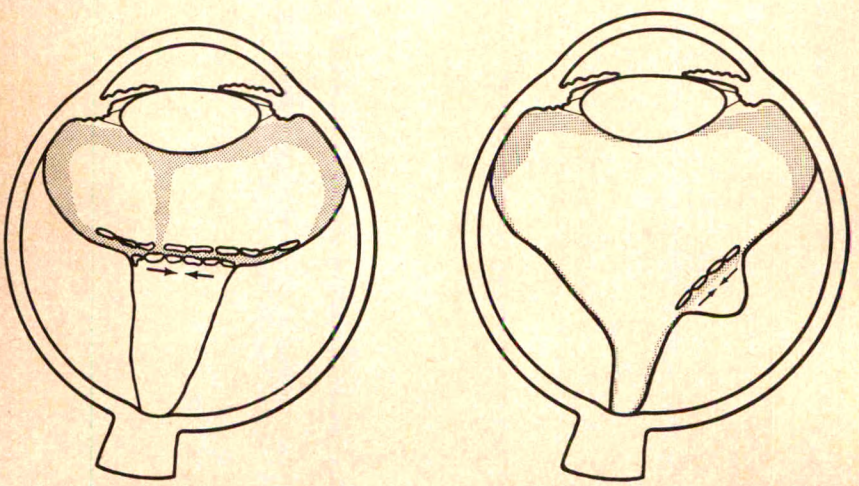


Fig. 20 (Laqua and Machemer). Fixed folds caused by contraction of intravitreal pigment epithelial membranes. Arrows indicate the main line of traction exerted by the contracting membrane (compare with Figure 3). Left, A circumferential fold is caused by pigment epithelial proliferation along a collagenous vitreous scaffold that is circumferentially adherent to the vitreous base and the peripheral retina. Right, Irregular folds develop when pigment epithelial cells proliferate along remnants of the posterior vitreous cavity that have partially detached from the retina (compare with Figure 4).

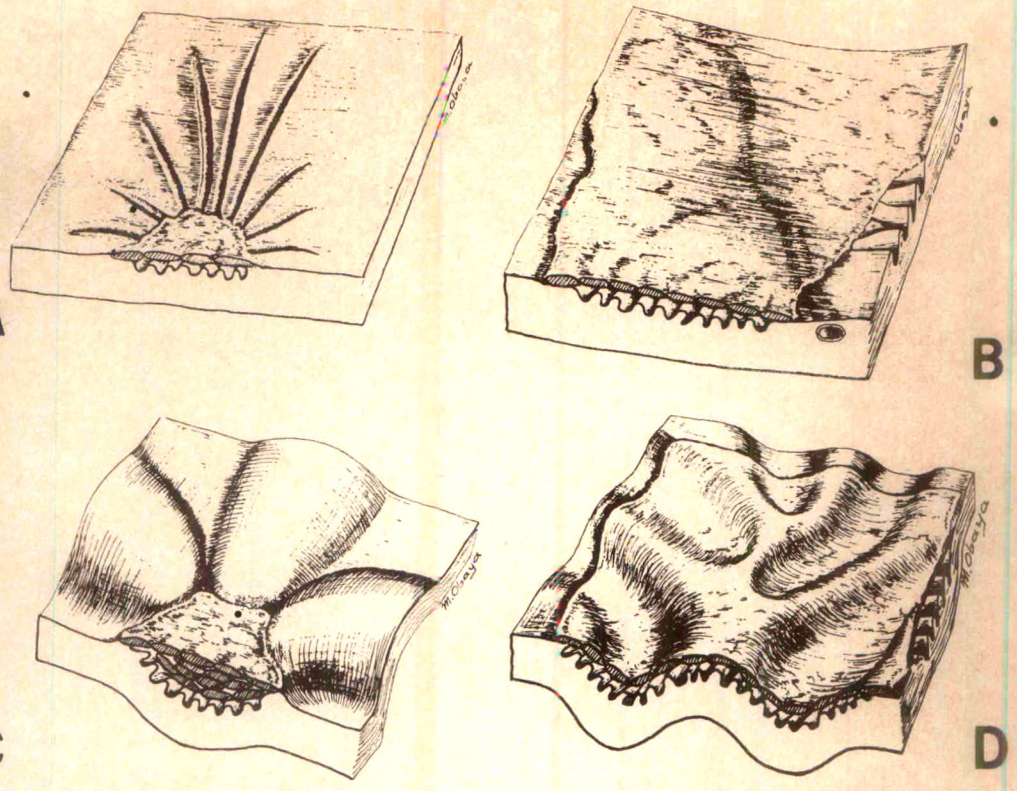


Fig. 21 (Laqua and Machemer). Fixed folds caused by contraction of preretinal pigment epithelium or glial membranes. A, Superficial starfolds are caused by localized and weak preretinal membranes exerting traction along the inner retinal surface (compare with Figures 5 and 6). B, Superficial irregular folding occurs in the presence of a more widespread but still weak preretinal membrane (compare with Figure 8). C, Heavy superficial folding due to contraction of a stronger preretinal membrane leads to a shortening of the inner retinal surface relative to the outer retinal surface and causes full-thickness folding of the retina toward the shortened side. If the proliferative process remains localized, a full-thickness starfold results (compare with Figure 7). D, More extensive preretinal membranes cause full-thickness irregular folds (compare with Figure 9).

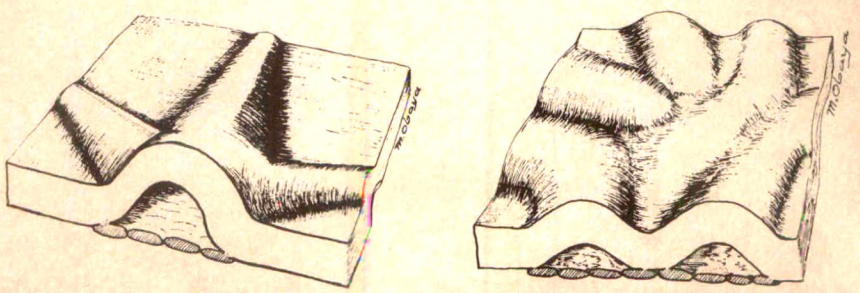


Fig. 22 (Laqua and Machemer). Fixed folds caused by contraction of subretinal glial membranes. Left, Full-thickness starfolds due to localized subretinal glial membranes with cellular connections to the outer retinal surface (compare with Figure 14). Right, Full-thickness irregular folds develop in the presence of more widespread subretinal glial membrane (compare with Figures 16, 17, and 19).

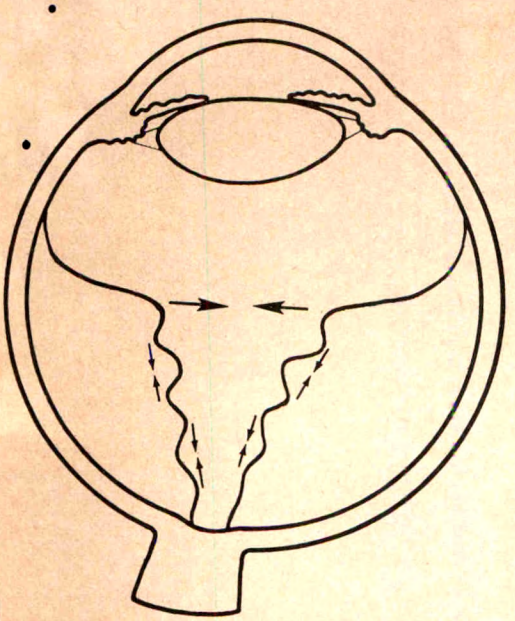


Fig. 23 (Laqua and Machemer). In end-stage MPP, fixed folds are caused by a combination of intravitreal, preretinal, and subretinal membranes. The arrows indicate the main direction of traction forces exerted by the periretinal membranes (compare with Figure 18).

eye.[10] The proposed mechanism causing this end-stage MPP is explained (Fig. 23) and will be discussed in more detail in a subsequent paper.

If one searches carefully, there is clinical evidence for some degree of this MPP process in nearly all eyes with retinal detachment. Often it is evident solely by the presence of intravitreal pigmented dots or semitransparent, immobile vitreous membranes. In only a few cases, the proliferative process causes fixed folds or, even more rarely, end-stage MPP. Unfortunately, no prognostic sign was found that would allow the clinician to determine which eye will eventually develop end-stage MPP. This negative result correlates well with our autoradiographic studies[1,2] which showed that the proliferative activity of pigment epithelial and glial cells demonstrate no predictable progression with time. Proliferative peaks seem to be most frequent around the fourth week after retinal detachment, but proliferation may continue in any eye over long periods of time.

Based on our histologic and clinical studies, we think of MPP as reactive cellular proliferation initiated by the separation of the retina from the pigment epithelium. It occurs to varying degrees in nearly all eyes with a retinal detachment, causing a multitude of well-defined clinical lesions.

Summary

In the owl monkey, proliferation of pigment epithelial and glial cells occurred in varying degrees in nearly all eyes with retinal detachments. These cells grew and formed membranes on all available intraocular structures in the posterior part of the eye, such as vitreous structures and inner and outer retinal surfaces. Clinically, this process covered a wide variety of lesions, including fixed retinal folds. Depending on the location, size, and extent of the pigment epithelial or glial membrane, different types of fixed folds occurred. In an exaggerated end stage of this proliferative process, a clinical picture may develop identical to what has been called massive vitreous retraction or massive preretinal retraction in humans. To emphasize the importance and ubiquity of cellular proliferations, we called this entity massive periretinal proliferation.

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OPHTHALMIC MINIATURE

Her small toad-like face looked even yellower than the day before. She was certainly ugly, and yet, like the toad, she had eyes like jewels, dark and imperious, revealing latent energy and an intellectual force that could be felt at once.

Agatha Christie, *Murder on the Orient Express*, 1934

CYSTIC RETINOBLASTOMA

JOSEPH GINSBERG, M.D., ABBOT G. SPAULDING, M.D., AND TAYLOR ASBURY, M.D.
Cincinnati, Ohio

Little information is available regarding cyst formation in retinoblastoma. The frequency, pathogenesis, and clinical significance of this phenomenon are virtually unknown. We, however, have had the opportunity to study a patient with a retinoblastoma, clinically simulating uveitis, in which a macro- and microcystic pattern was prominent. The unusual findings in our patient prompted us to investigate cystic changes in other cases of retinoblastoma.

CASE REPORT

An 8½-year-old black boy developed persistent redness and irritation of the left eye after a hot water burn. Reinjury with a baseball 1½ months later resulted in severe pain and decreased vision. Two months after the initial trauma, examination revealed a fluffy, grayish-white exudate partially filling the anterior chamber and accompanied by rubeosis iridis. The fundus was obscured. Visual acuity was limited to inaccurate light projection. Ocular pressure was 64 mm Hg by Schiøtz tonometry. The diagnoses were traumatic iritis, hypopyon, and secondary glaucoma.

The patient failed to improve with topical and oral corticosteroids and cycloplegics. Cultures of the iris and aqueous were negative. The cells in the aspirate were thought to be leukocytes.

The anterior segment remained essentially unchanged (Fig. 1), but a whitish mass became visible in the hazy vitreous body. Roentgenograms suggested calcium deposits in the blind left eye. Approximately 3½ months after the initial trauma, enucleation was performed because of the possibility of retinoblastoma.

The globe measured 25 mm in each of its three principal meridians; the optic nerve stump measured 4 mm. Flocculent, pinkish-gray material filled about one third of the anterior chamber. A horizontal section revealed the retina to be totally detached and diffusely thickened by a grayish-white neoplasm. The lesion was more prominent posteriorly where it contained coalescent cysts (Fig. 2), the largest (4 to 5 mm) projecting toward the subretinal space which contained an abundance of grayish-green, slightly hemorrhagic fluid. Particulate matter and sheets of tumor occupied the vitreous remnant and partially surrounded the lens and ciliary body (Fig. 2).

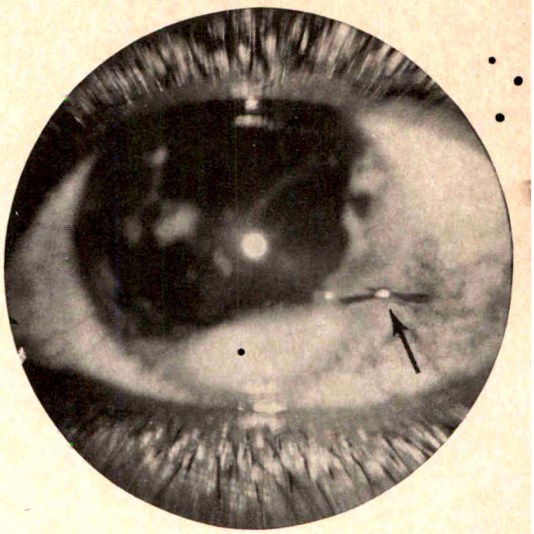


Fig. 1 (Ginsberg, Spaulding, and Asbury). Pseudohypopyon due to retinoblastoma in anterior segment. Suture (arrow) indicates site of diagnostic iridectomy and aqueous aspiration.



Fig. 2 (Ginsberg, Spaulding, and Asbury). Grossly visible cysts (arrows) projecting toward the subretinal space. Retinoblastoma has spread to vitreous and anterior segment.

From the University of Cincinnati College of Medicine, Cincinnati, Ohio. This study was supported in part by the Ohio Lions Eye Research Foundation.

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The eye was fixed in 10% formalin, embedded in paraffin, and sectioned at approximately 8 μ; stains were hematoxylin and eosin, PAS, and Alcian blue. Approximately 85% of the retina was infiltrated by a neoplasm extending to the lamina cribrosa and to all neuronal layers, but more or less sparing the periphery, macular, and disk areas. Except for a few, scattered foci showing what appeared to be photoreceptor differentiation, the tumor comprised relatively uniform, diffusely distributed cells with hyperchromatic nuclei and scant cytoplasm. Mitoses were frequent. Because of the characteristic cytology, a diagnosis of retinoblastoma seemed justified.

The cysts, grossly apparent within the tumor, extended into the subretinal space (Fig. 3). They contained deeply eosinophilic precipitate similar to that noted in the subretinal area. Cyst walls were thin, in some areas only one or two cell layers thick.

In addition to the larger cysts, there were many ovoid, round, or irregular microcysts, some confluent, and others partially separated by septa; a sinusoidal pattern prevailed (Fig. 3). Occasional free elements in the lumen resembled photoreceptors (Fig. 4). The precipitate in microcysts was sparse and mainly in the form of fine or coarse strands (Fig. 3). Lining cells appeared identical to those elsewhere in the tumor. Their nuclei were often compressed, staining darker than adjacent cells, and tended to have a circumferential orientation.

There was an unusually prominent vasoproliferative component, especially on the medial aspect. This was characterized either by solid clumps of endothelium or more mature vessels with walls seven to eight layers thick. Intracystic proliferation of endothelium appeared in about 10% of the smaller cysts (Fig. 5).

Partially necrotic clusters of neoplastic cells lay in the anterior chamber, and a few leukocytes (mainly lymphocytes) appeared in the iris stroma that was deeply invaded by tumor. A fibrovascular membrane on the anterior iris surface resulted in ectropion uveae and peripheral synechiae.

Three years after enucleation there was no recurrence of the retinoblastoma.

Discussion

A cystic appearance in retinoblastoma is rarely described,[1-3] although cysts have been noted microscopically in several cases. We reviewed the 44 retinoblastoma cases (35 patients) in our files and noted microcysts in 20 (45%). These numbered from one to 20 per scanning lens field and averaged about 200 μ in diameter, the largest being

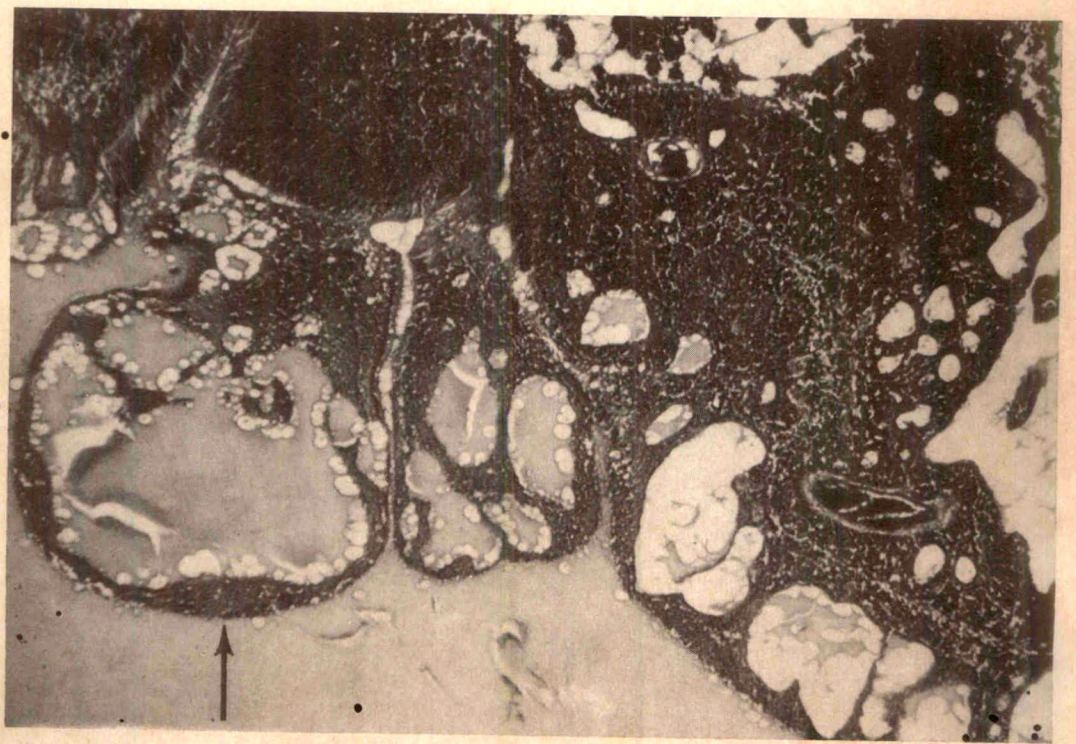


Fig. 3 (Ginsberg, Spaulding, and Asbury). Extensive distribution of cysts in a retinoblastoma. Microcysts afford a sinusoidal appearence. Much proteinaceous precipitate appears in a macrocyst (arrow) projecting into the subretinal space (hematoxylin and eosin, ×21).

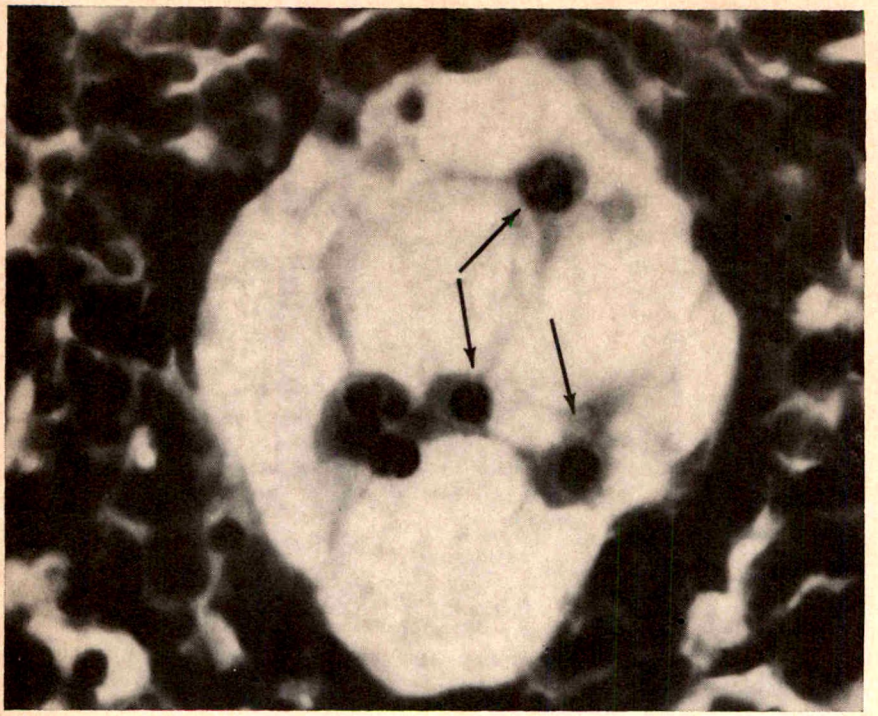


Fig. 4 (Ginsberg, Spaulding, and Asbury). Microcyst-containing cells (arrows) suggesting photoreceptor differentiation (hematoxylin and eosin, ×450).

3 mm. In only two or three cases did it appear that they could have been detected macroscopically.

Cystic retinoblastoma has been recorded clinically, but rarely.[4-7] The larger cysts in our patient might have been observed clinically if the media had been clear. In a recent report[8] the "cystic" retinoblastoma visualized by B-scan ultrasonography appeared to be recognized by ophthalmoscopy with greater difficulty than the solid variety. Current knowledge and our own cases suggest that clinically or grossly visible cysts may be evident in about 5% of retinoblastomas.

The pathogenesis of cystic retinoblastoma is unclear and there appears to be no correlation with the growth pattern, degree of differentiation or size of the neoplasm, or with its location. Ts'o, Zimmerman, and Fine[3] noted microcystic spaces in foci exhibiting photoreceptor differentiation. On the other hand, most of the cysts in our patient, and in those we reviewed, occurred in relation to undifferentiated neoplasm. We found no structural variation suggesting different mechanisms for the development of large or small cysts; the latter may expand or coalesce to form macrocysts.

The nature of the vascularization in the tumor may be related to cyst formation. The degree is probably less significant than abnormalities of blood vessel development or capillary obliteration. In our patient and in 13 (65%) of those we examined, incompletely canalized or obliterated capillaries were contiguous with or within the lumen of about 10% of microcysts. This suggests that ischemia may be a factor in cyst formation, the fluid-filled cysts possibly representing a result of liquefactive necrosis. Coagulative necrosis is more frequent in retinoblastoma, and both are probably related to vascular insufficiency. Calcification may also be associated with cyst formation; calcium was deposited adjacent to or within the

lumen of larger cysts in four (20%) of our cases.

The fluid in the cysts often resembled that in the subretinal region. In a few instances it stained weakly with PAS and Alcian blue; in the cases studied by Ts'o, Zimmerman, and Fine,[3] the fluid did not react to these stains. In our patient, the cells lining cysts were similar to those comprising the remainder of the tumor. There is no evidence that retinoblastoma cells have a secretory capacity. In our patient, possibly the

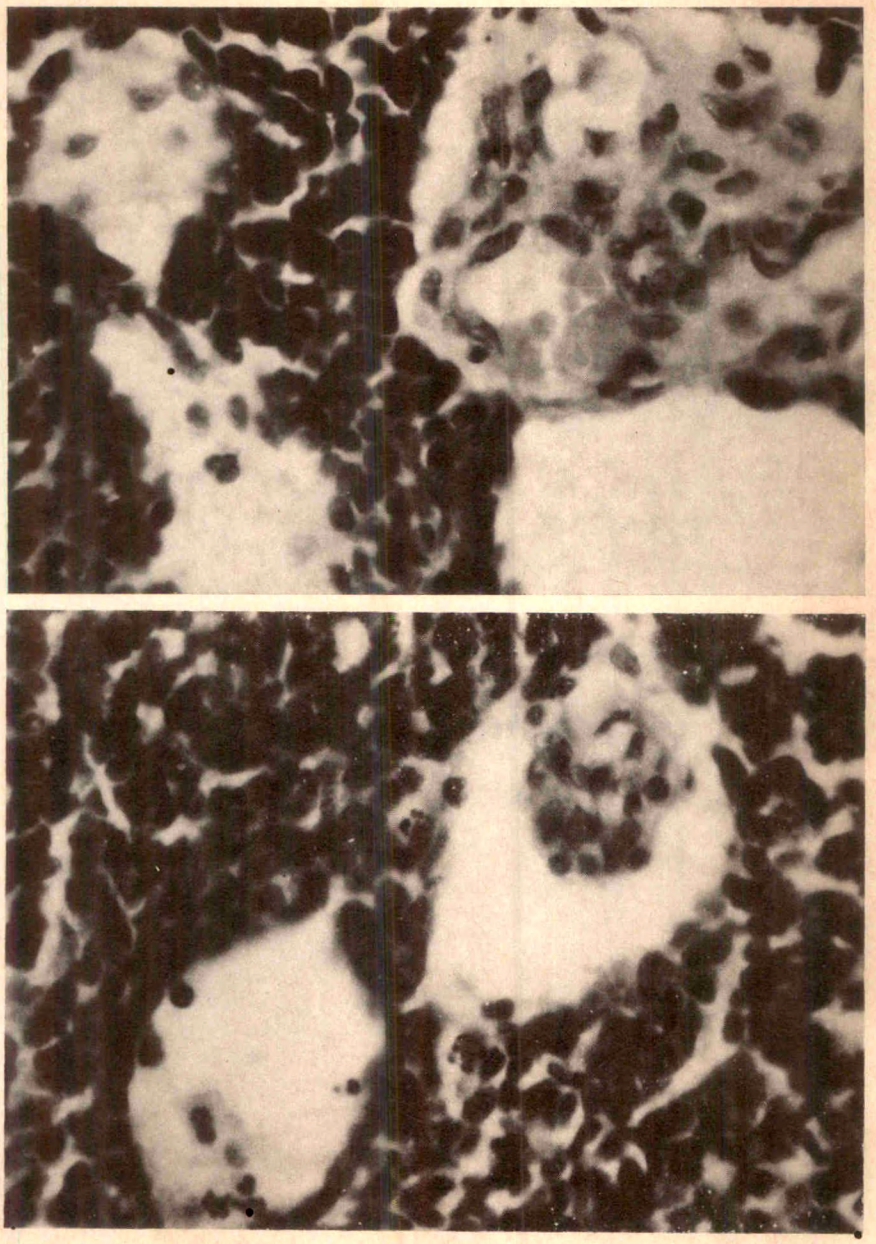


Fig. 5 (Ginsberg, Spaulding, and Asbury). Top, Capillary buds contiguous with microcysts. Bottom, Capillary growing in lumen of microcyst. Note incomplete canalization or obliterated appearance (hematoxylin and eosin, ×270).

paracentesis and the two episodes of trauma were partially responsible for the production of fluid in the cysts. Some of it may have seeped in from the subretinal space.

The prognostic significance of the cystic phenomenon in retinoblastoma is unknown. In a recent case of spontaneous regression of bilateral retinoblastoma,[7] an intraretinal cyst was noted in one of the affected eyes.

Cystic and vascular alterations, similar to those in our case, are common in extraocular neoplasms including those of the central nervous system.[9]

The growth pattern in the retinoblastoma in our patient did not conform with the three classical varieties, that is, exophytic, endophytic, or the planum types (diffuse infiltrating retinoblastoma). Apart from its grossly visible cysts, however, the tumor was comparatively flat and diffuse in its distribution, thus suggesting a variant of the diffusely infiltrating type. This is the least common form and tends to simulate uveitis, usually with "hypopyon" and secondary glaucoma. This occurs even when there is no recognizable thickening of the retina.[10,11] Optic nerve involvement was lacking in our case; nerve involvement has been reported in only one case.[12]

Most cases of diffuse infiltrating retinoblastoma have occurred in boys between the ages of 6 and 11 years,[13] like our patient. Retinoblastomas in children older than 4 years old have unusual manifestations.[14]

Delay in diagnosis and enucleation in our patient was the result of the "atypical" clinical manifestations and a misinterpretation of the cells in the aqueous aspirate. A careful evaluation of particulate matter in the anterior chamber is essential whenever retinoblastoma is suspected, using the Papanicolaou stain or electron microscopy, before a negative report is rendered.[14]

Summary

A grossly cystic retinoblastoma, presumably a form of the diffuse infiltrating type, mimicked uveitis in an 8½-year-old boy. A review of 44 cases indicated that grossly (clinically) detectable cysts are rare in this neoplasm, although microcysts are relatively common.

Lesions of this nature, especially if presenting with a history of trauma, as in our patient, may lead the ophthalmologist to diagnose uveitis. The diagnosis of retinoblastoma may thus be unduly delayed.

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RETINAL FAT EMBOLI AS A SEQUELA TO ACUTE PANCREATITIS

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Fat embolism is not uncommon in many organs in cases of acute pancreatitis. However, the ocular manifestations of acute pancreatitis have not been previously recognized. Three patients with acute pancreatitis developed a fundus picture compatible with Purtscher's retinopathy.

Fat emboli in the retina present as multiple cotton-wool spots around the optic nerve head, often confluent and usually not extending past the macula. These are usually accompanied by varying numbers of superficial hemorrhages. Most cases present bilaterally, but uniocular cases have been reported. Initially, there are field defects and a decline in visual acuity; the course is, however, variable. The condition is generally associated with trauma, and is thought by many to be the same as Purtscher's[1] angiopathic retinopathy.

Fat emboli are found in many other organs besides the eye, including the brain, lungs, heart, and kidneys.[2] While the most common source is intramedullary fat in long bone fractures,[3,4] emboli also occur after surgical trauma to fatty areas[4,5] and after injections of oily materials and paraffins.[6] They also appear in acute pancreatitis, presumably due to enzymatic destruction of omental adipose tissue.[7,8]

CASE REPORTS

Case 1—A 40-year-old man was admitted Aug. 28, 1974, with a three-day history of epigastric pain, vomiting, and diarrhea. Past medical history included excessive drinking for many years.

Physical examination revealed an agitated man in delirium tremens. The pupils were moderately dilated and responded sluggishly to light. The ocular fundi were unremarkable.

Laboratory studies disclosed the following values: serum amylase, 860 dye units/100 ml (normal, 45-200); and urinary amylase, 1,876 mg/1000 ml. On awakening, he complained of decreased vision. On the sixth hospital day, visual acuity was finger counting at 3 feet in each eye. Pupils were round, 5 mm in diameter, and reacted sluggishly to light. The anterior segments were normal. Ophthalmoscopic examination revealed a large confluence of cotton-wool spots surrounding each disk and extending temporally, giving the appearance of a cherry-red spot in each macula (Fig. 1). The white mounds were superficial and, in places, obscured the larger retinal vessels. There were superficial flame-shaped hemorrhages in each fundus.

On Sept. 8, fluorescein angiography in the left eye revealed nonfilling of several macular arterioles 0.5 disk diameter off the disk at 3 o'clock, and 1 disk diameter from the disk at 1:30 o'clock (Fig. 2). Capillary perfusion was absent between the disk and the macula. In a 2-disk diameter area, peripapillary superficial hemorrhages were demonstrated as several small areas of blocked fluorescence. No leakage was observed in the late phases. A similar picture was present in the right eye. The area of arteriolar nonfilling and capillary nonperfusion, however, was less extensive.



Fig. 1 (Inkeles and Walsh). Case 1. Right eye. The inner portion of the sensory retina surrounding the optic nerve is partially opacified by confluent whitish areas. Superficial retinal hemorrhages are present.

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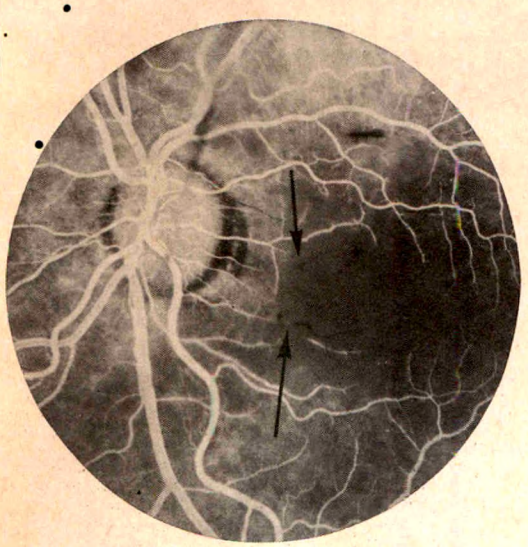


Fig. 2 (Inkeles and Walsh). Case 1. Left eye in the venous phase. Nonfilling of several arteries is noted (arrows). Large areas of capillary nonperfusion are present, most marked between the disk and the macula.

On Sept. 17, there was slight clearing of the exudates. Visual acuity was finger counting at 3 feet in both eyes. By Nov. 21, all of the cotton-wool spots had disappeared but visual acuity had only improved to R.E.: 20/200, and L.E.: 6/200.

Case 2—A 26-year-old woman presented on Sept. 24, 1973, with a complaint of blurred vision in both eyes for one week. Previous ocular history was unremarkable. Eleven days previously she had been hospitalized for five days with acute pancreatitis occurring after alcoholic abuse.

Visual acuity was R.E.: 20/25, and L.E.: 20/30. At the posterior pole in each eye, a normal optic disk was surrounded by multiple cotton-wool spots and a few flame hemorrhages, extending to 2 disk diameters. These changes were most marked in the area between the disk and macula (Fig. 3).

A fluorescein angiogram demonstrated multiple small areas of capillary nonperfusion, temporal to both disks and extending somewhat beyond the maculae. A few small areas of blocked fluorescence were present, representing superficial hemorrhages. In the late phases, mild intraretinal leakage occurred (Fig. 4). The patient was lost to follow-up.

Case 3—A 34-year-old man presented on Sept. 21, 1961, with a history of painless blurred vision in both eyes for several weeks. He was a heavy drinker who had recently been discharged from another hospital with the diagnosis of acute pancreatitis and delirium tremens.

Corrected visual acuity was 20/50 in both eyes. Findings were confined to the posterior pole. The disks appeared hyperemic but flat. The arteries were burnished with some slight nicking at the arteriovenous crossings. Multiple cotton-wool spots were present throughout the posterior poles, extending to just beyond the maculae. Some superficial flame hemorrhages were also noted in the same distribution (Fig. 5). The peripheral retinas were unremarkable. Fluorescein angiograms were unavailable. The patient was lost to follow-up.

Discussion

In 1910, Purtscher[1] described posttraumatic retinal changes consisting of multiple

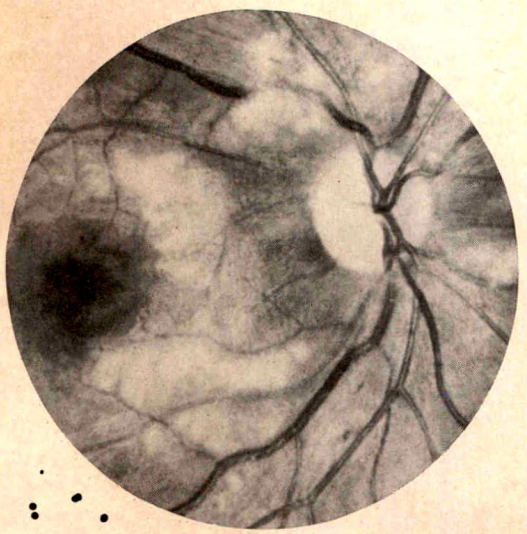


Fig. 3 (Inkeles and Walsh). Case 2. Right eye. Superficial white fluffy patches are scattered throughout the posterior pole. Superficial retinal hemorrhages are present.

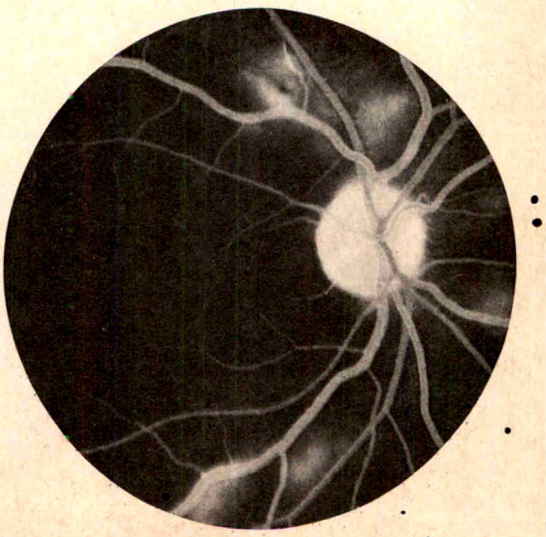


Fig. 4 (Inkeles and Walsh). Case 2. Right eye in the late phase. Scattered areas of intraretinal leakage of fluorescein are present in the posterior pole.

white spots with scattered hemorrhages. He ascribed the changes to a sudden increase of cerebrospinal fluid pressure. Stähli[9] and Best[10] felt the condition was similar to Berlin's edema and due to a sudden increase in venous pressure. However, Urbanek,[11] in 1934, provided the first clinicopathologic correlation of traumatic retinopathy and fat emboli by demonstrating fat in both retinal and choroidal vessels. He proposed that this was the cause of Purtscher's retinopathy. Additional clinicopathologic studies[12–14] of Purtscher's retinopathy have been published, demonstrating fat emboli in retinal and uveal vessels.

These reports seem to establish fat emboli as the most probable explanation of Purtscher's retinopathy. In 1964, Ashton and Henkind[15] produced cotton-wool spots and superficial hemorrhages experimentally, using glass emboli of various diameters. Yet, despite both pathologic and experimental evidence for emboli as the cause of Purtscher's retinopathy, the presence of this picture after traumatic incidences that did not involve fractures led some to question whether a concurrent or separate physiologic process might be involved. Marr and Marr,[16] Spaeth,[17] Madsen,[18] and Duane[19] proposed causes based on vessel damage secondary to suddenly increased intraocular venous pressure. While plausible, this has yet to be demonstrated clinicopathologically.

The presence of fat emboli in a patient who died of acute pancreatitis was first reported by Edmondson and Fields[7] in 1942. The patient was a 48-year-old man who died nine hours after admission to the hospital with the clinical diagnosis of acute pancreatitis. The peripancreatic tissue had severe necrosis with both calcium soaps and free fat present. The omental venules and lymphatics had free fat within their lumina. The lungs had many vessels with fat droplets, ranging from the size of a platelet to those so large as to occlude the capillary completely. The heart was similarly involved. The eyes were not mentioned.

In 1954, Lynch[8] stained for fat in two cases of acute pancreatitis and demonstrated fat emboli in the heart, lung, and brain. In another patient who died after a period of recovery, the kidneys were fibrotic and Lynch[8] speculated that the original insult had probably been fat emboli.



Fig. 5 (Inkeles and Walsh). Case 3. Left eye. Superficial white areas are present throughout the posterior pole and several superficial hemorrhages are present. The dark spots just inferior to the disk are artifacts from the old carbon-arc fundus camera.

There have not been any reported fluorescein angiograms in patients who were later proven to have fat emboli in the eye at autopsy. There have been several studies of patients with the clinical picture of Purtscher's disease after trauma. Amalric and Bonnin[20] cited a case that showed small areas of arteriolar occlusion. Kelly[21] demonstrated areas of leakage without areas of nonperfusion. Gass[22] reported a case in which white material lay between and also anterior to the retinal vessels. There were superficial hemorrhages, areas of capillary nonperfusion, and other areas in which the capillary bed was obscured by the white lesion. There was late leakage in the retina. Gass felt the confluent appearance and superficial location of the exudate made it different from the typical cotton-wool patches caused by embolic infarction. He concluded that they were the result of exudates forcibly

extruded from the retinal vessels. He also felt that much of the loss of transparency was due to edema of the perivascular retinal cells.

Both of our patients who had fluorescein angiography showed areas of retinal arteriolar and capillary nonperfusion and obscuration of the background fluorescence as described by Gass.[22] We propose that embolic phenomena explain this angiographic finding. Ashton and Henkind[15] showed that emboli could produce cotton-wool type lesions in the nerve fiber layer at the posterior pole. The occlusion of many small posterior polar arterioles could account for the areas of nonperfusion as well as the massive confluence of cotton-wool spots that could obscure retinal vessels. Ashton and Henkind[15] also noted that retinal edema accompanied the emboli. Initially it was a slight haze but later in the first week it became dense white and well delineated from the unaffected surrounding tissue. Both the confluent cotton-wool spots and this dense white edema are present in our patients.

In our three patients, the ophthalmoscopic appearance of large areas of confluent cotton-wool spots and superficial hemorrhages is best explained by occlusion of small arterioles and capillaries. This theory was proposed in 1961 by G. N. Wise (unpublished data). The fluorescein angiograms lend support to this conclusion in the two cases in which this diagnostic test was performed. The experimental work of Ashton and Henkind,[15] occluding arterioles with glass beads, produced a clinical result essentially identical to our cases. Their subsequent pathologic studies showed the obstruction was at the arteriolar level with loss of capillary bed in the area originally supplied by the obstructed vessel.

Summary

A clinical picture of Purtscher's retinopathy was observed in three patients with acute pancreatitis. In two patients, fluorescein angiography revealed arteriolar obstruction. Since fat emboli occur in pancreatitis, and since fat emboli may produce the picture of Purtscher's retinopathy, we proposed that fat emboli caused the retinal findings in these patients.

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POSTERIOR VORTEX VEIN AND CONGENITAL GLAUCOMA IN A PATIENT WITH TRISOMY 13 SYNDROME

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Ocular defects in the trisomy 13 syndrome are well known. Few of these eyes have been followed clinically since the infants are short-lived and the eyes are so affected as to preclude therapy. An infant with trisomy 13 syndrome exhibited bilateral congenital glaucoma; one eye also exhibited a rare posterior vortex vein.

CASE REPORT

This infant boy, weighing 2,660 g (5 lbs, 15 oz), was the product of a 23-year-old woman, gravida 5, para 1, abortus 4. There were no abnormalities during the 40-week pregnancy and the labor and delivery were normal. The child had an abnormal facial appearance and polydactyly of both hands and one foot (Fig. 1). Because of a midline cleft palate, the child also had difficulty eating.

At 11 days of age the child was operated on because of a patent omphalomesenteric duct. After discharge from the hospital at 16 days of age, the child gained weight slowly, weighing 4,480 g (10 pounds) at 4 months of age. He had a chronic cough and occasionally experienced periods of apnea that were self-limited. At 4 months of age the child had corneal clouding in both eyes and was referred here for evaluation.

Physical examination revealed the following values: weight 4,740 g; pulse rate, 140 beats per minute; respiration rate, 36; and head circumference, 36 cm. (All of these measurements are normal for a 2-month-old child.) The forehead was flattened, and there was a large anterior fontanelle. The nasal bridge was markedly flat with prominent nares. A cleft of the soft and hard palates was present in the posterior part of the palate. There were coarse rhonchi throughout his lung fields. The heart had a grade 3 holosystolic murmur that was loudest in the left sternal border. The liver and spleen were not enlarged. The penis was small. Supernumerary digits had been present on the postaxial side of the hands and the right foot. At 5 months of age, the child did not have a grasp and had poor head control. Although the child reacted to pain, he did not spontaneously react to his parents. Laboratory studies showed a normal blood cell count. An x-ray film examination revealed flattening of the acetabular angles bilaterally. The vertebral bodies in the thoracic and lumbar areas showed flattening. This child had a karyotype of 47 XY + D (Fig. 2). The extra D chromosome was identified as a 13 chromosome by fluorescent staining of the chromosome. The clinical picture was compatible with the karyotypic analysis.

Visual acuity was light perception in both eyes. Pupils responded normally to direct and consensual

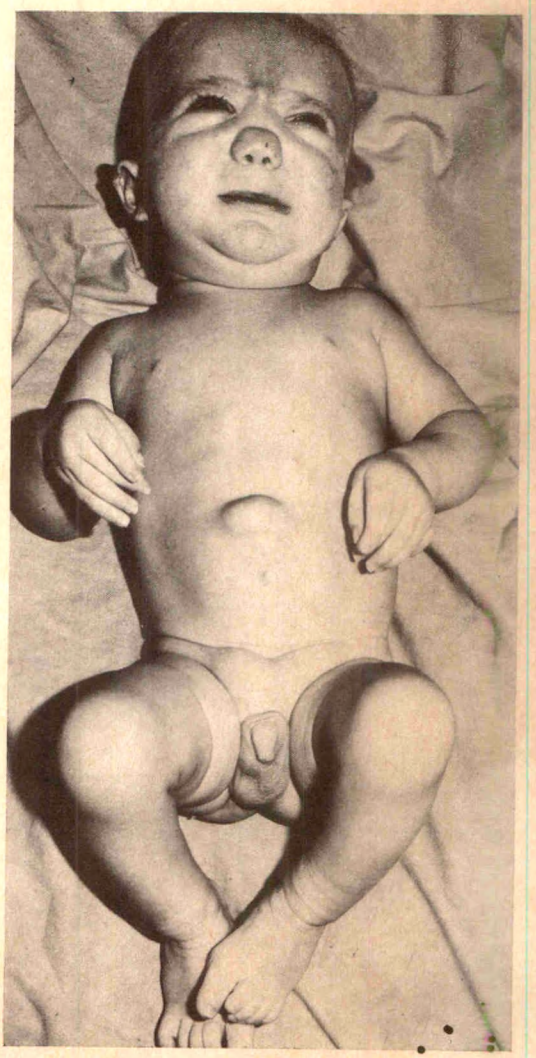


Fig. 1 (Lichter and Schmickel). Infant has ventral hernia, crossing of index finger over middle finger, and a left hand with supernumerary digits.

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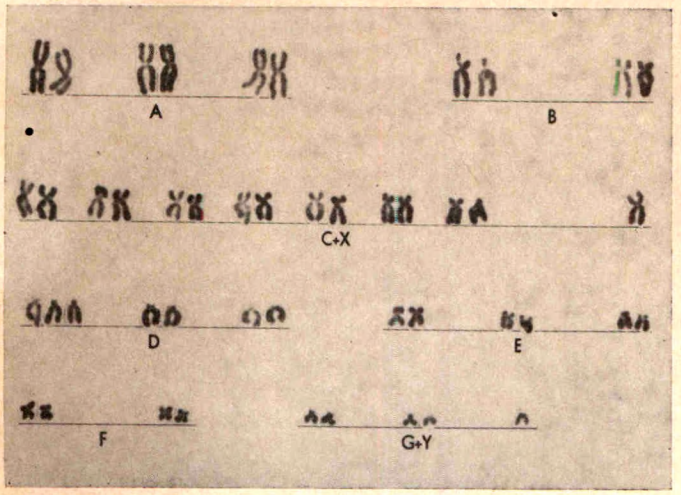


Fig. 2 (Lichter and Schmickel). This karyotype, made from the patient's leukocyte count after three days in culture, shows an extra 13 chromosome.

stimulation. No abnormality of ocular motility was noted. Using ketamine, we performed an ocular examination under anesthesia. Both globes were white. The corneas measured 13 mm in diameter horizontally and revealed moderate epithelial edema. Tears were present in Descemet's membrane. The anterior chambers were deep and clear. Irides were blue. The appearance of the pupils was normal. The lenses appeared normal.

Intraocular pressure was R.E.: 59 mm Hg and L.E.: 40 mm Hg by Schiøtz tonometry. Gonioscopy revealed wide-open angles with iris insertion into the ciliary body. There was no angle recess (Fig. 3). No iris processes were seen. Prominent radial and circumferential iris vessels were considered to be normal vasculature. The right optic disk was nearly totally cupped (Fig. 4, left). The fundus was pale but was otherwise unremarkable. The left optic disk showed a 0.6 to 0.7 cup/disk ratio (Fig. 4, right). Just temporal to the disk a large choroidal vessel had the appearance of a vortex vein (Fig. 5). The major trunk of the vessel appeared to disappear into the sheath of the optic nerve. The reminder of the ophthalmoscopic examination was unremarkable.

We diagnosed bilateral congenital glaucoma and a goniotomy was performed in each eye without difficulty.

Using ketamine, we performed an examination during anesthesia at 5 months of age. The corneas were clear. Corneal diameters were R.E.: 14.0 mm, and L.E.: 13.5 mm. Intraocular pressure was R.E.: 22 mm Hg, and L.E.: 15 mm Hg. Both goniotomy clefts were open. The appearance of the optic disks was similar to the initial examination.

At 8 months of age the child responded to light with either eye. The pupils responded normally. Another examination was performed during anesthesia using ketamine. Intraocular pressure by Schiøtz tonometry was R.E.: 11 mm Hg, and L.E.: 19 mm Hg. The corneas were clear. Gonioscopy was unchanged. The right optic disk showed a 0.5 cup/disk ratio, a definite improvement. The left optic disk was totally cupped. Retinoscopy revealed the following: R.E.: plano, L.E.: —6.00 sphere. The patient was lost to follow-up.

Discussion

Ocular findings are nearly always encountered in the trisomy 13 syndrome and are generally extensive. Most commonly, these eyes show microphthalmos, coloboma, retinal dysplasia, cataract, and occasionally

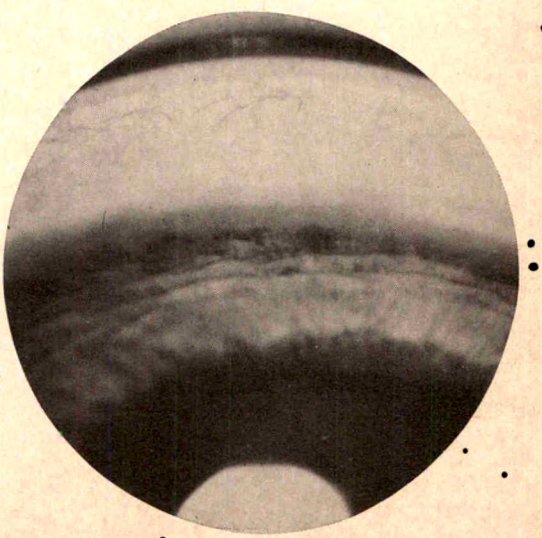


Fig. 3 (Lichter and Schmickel). Goniophotograph showing wide-open angle. This photograph was taken after goniotomy and shows the cleft on the right side of the photograph.

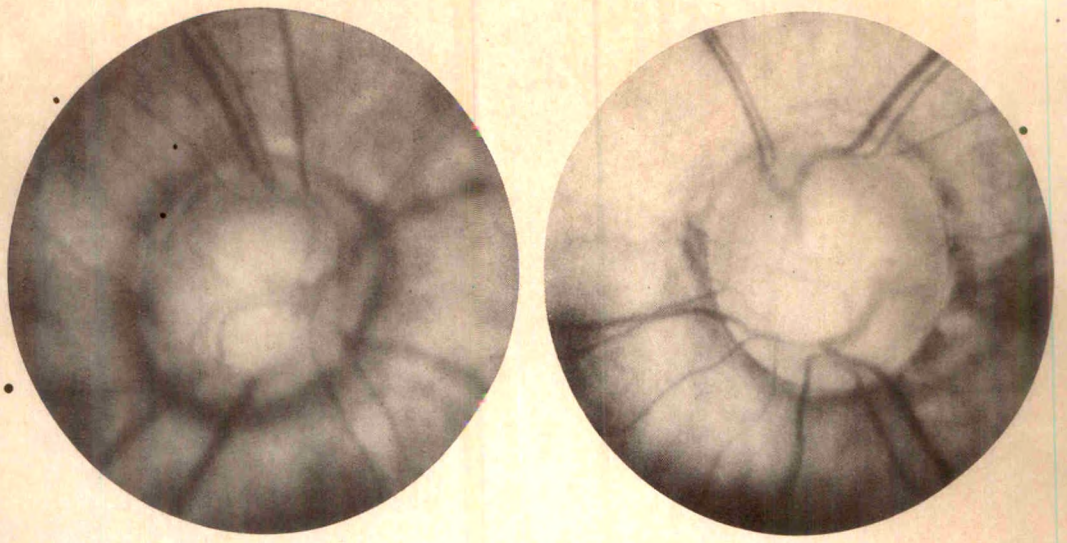


Fig. 4 (Lichter and Schmickel). Left, The right optic disk showing nearly total glaucomatous cupping. Right, The left optic disk with nearly total cupping. A large choroidal vein is visible near the temporal edge of the disk.

intraocular cartilage. Keith[1] described a case of congenital glaucoma in a patient who was operated on and the eyes were examined histologically later. Extensive cupping was present in the optic disks. Keith indicated that the extent of ocular involvement in trisomy 13 syndrome appears to be related to the degree of systemic manifestation.

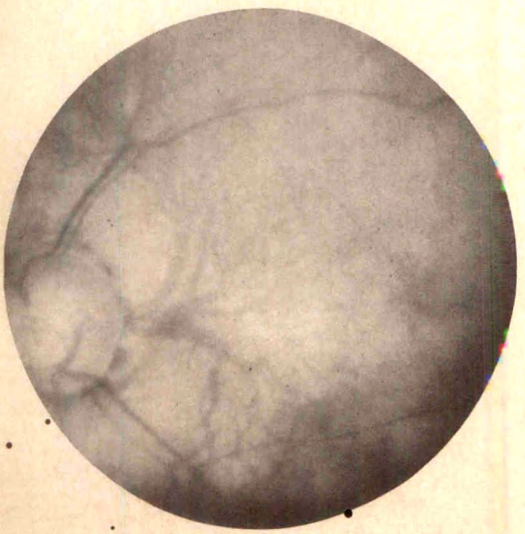


Fig. 5 (Lichter and Schmickel). Left ocular fundus showing the large posterior vortex vein reaching the margin of the optic disk.

Recently other findings have been reported in trisomy 13 syndrome. Hoepner and Yanoff[2] reported retention of nuclei in the lens nucleus and reticular cystoid degeneration in a posterior portion of the retina, and emphasized the frequency of mesodermal dysgenesis of the anterior segment. Rodrigues, Valdes-Dapena, and Kistenmacher[3] described trisomy 13 syndrome in a patient with hypopigmentation of the retinal pigment epithelium in one eye. Ginsberg and Bove[4] reported four cases of trimsomy 13 syndrome that suggested two types of ocular involvement. The first, most frequent and most severe, included microphthalmos, vitreoretinal hyperplasia, detachment, and coloboma. The second type demonstrated minor defects in normal-size eyes. One of the patients in this report demonstrated apparent pathologic cupping of the optic disk, suggesting glaucoma.

Congenital glaucoma occurred in our patient who had trisomy 13 syndrome with a posterior vortex vein, a rare occurrence.

Mann[5] called such veins posterior vortex veins. The appearance and function of such vessels make such a name appropriate. Mann indicated that these veins turned over the

edge of the disk to drain into veins within the sheath of the optic nerve and then into the ophthalmic vein. Mann felt that although such veins were only seen in myopic eyes, these might be due to the stretching of these eyes which simply made these veins more easily visible. She said such veins were of no diagnostic or morphologic significance.

Duke-Elder and Wybar,[6] who called these veins choriovaginal veins, stated they passed through the sclera close to the optic disk and terminated in the distal aspects of the pial venous plexus of the optic nerve. Thereby, a communication was established between the choroid and intraneural portion of the central retinal vein. Again, the predominant occurrence in myopic eyes was stressed.

The present case illustrates a posterior vortex vein in trisomy 13 syndrome with congenital glaucoma. Although the eye illustrating the venous anomaly was moderately myopic, this eye was myopic secondary to the glaucoma. Although the glaucoma was bilateral, it was more severe in this, the left eye. This finding represents an anomalous development of choroidal circulation.

Summary

A 4-month-old infant boy presented with a mild manifestation of trisomy 13 syndrome. The severe ocular findings usually associated with this syndrome were not seen. Rather, the patient had bilateral congenital glaucoma with glaucomatous optic disk cupping and, in one eye, a posterior vortex vein. Such findings are unusual in the trisomy 13 syndrome. The posterior vortex vein is a particularly unusual finding previously occurring in myopic eyes.

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PARANASAL SINUS CARCINOMA CAUSING ORBITAL MUCOCELE

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Mucoceles account for 3 to 4% of orbital tumors.[1] This diagnosis, when proven in cases of unilateral proptosis, traditionally provokes a sigh of relief from all concerned. Longevity is relatively unthreatened, and, with proper surgical attention, the prognosis is excellent. Recent experience with three patients, however, has changed our attitude toward this usually benign tumor. In each of these instances a typical frontal sinus mucocele extending into the orbit was the presenting picture of an otherwise asymptomatic squamous cell carcinoma.

CASE REPORTS

Case 1—A 68-year-old woman was first seen in May 1971 complaining of vertical diplopia. She was in good health until 1969 when asymptomatic proptosis of the left eye was noted on a routine ophthalmologic examination. Skull x-ray films and orbital tomograms were negative. A radioactive iodine uptake test was normal and showed borderline suppression after liothyronine sodium (Cytomel). Her presumed diagnosis was thyroid ophthalmopathy.

Later in 1969 she developed intermittent vertical diplopia. One year later it was almost constant and she consulted another ophthalmologist who noted 6 mm of proptosis and some congestion of her conjunctival vessels on the left side. She was advised to use an occluder over one eye.

On May 17, 1971, corrected visual acuity was 20/15 in both eyes. There was mild blepharoptosis and 6 mm of proptosis on the left (Fig. 1, top). The left eye was somewhat downwardly displaced, and fullness was noted in the upper nasal aspect of the orbit. The ocular motility was full but for marked restriction of movement of the left eye up and in (Fig. 1, bottom). The pupils, visual fields, and slit-lamp examination were normal. Dilated indirect ophthalmoscopic examination revealed a few striae in the extreme upper nasal quadrant of the left fundus.

A review of photographs taken in 1954 showed no exophthalmos. However, proptosis of the left eye was definitely present in 1964, and further photographs documented progression over the next three years. Skull x-ray films showed clouding of the frontal sinus and destruction of the superior medial rim of the left orbit. Orbital venography showed an anteromedially placed left orbital mass.

In June 1971, the left orbit was explored, and a typical frontal sinus mucocele was found, incised, and drained. Postoperatively the proptosis decreased to 1 mm, and the vertical diplopia disappeared. Within one year, however, she had a recurrence of 4 mm of proptosis, and she was referred to an otolaryngologist who resected the mucocele in May 1972. Biopsy material for histologic examination was taken from the defect in the floor of the sinus and from the wall of the mucocele. This was reported as orbital mucocele.

Although the proptosis disappeared, she complained of persistent pain behind the left eye. This led to a partial ethmoidectomy and removal of one turbinate in May 1973; an antrostomy in February 1974; and an osteosinusectomy and antrostomy in June 1974. These procedures did not relieve her pain.

On Sept. 23, 1974, she presented for neuro-ophthalmologic reevaluation because of the persistent pain behind the left eye. There was 2 mm of proptosis on the left and hypesthesia over the first and second trigeminal divisions on the left side. Skull x-ray films and orbital tomograms showed a recurrence of the mucocele, this time more posteriorly in the left orbit. Because of the protracted painful course in this patient, the pathology was reviewed. Sections from the bone around the defect in the floor of the frontal sinus taken at the second operative procedure showed definite invasive squamous cell carcinoma (Fig. 2).

Neurosurgical consultation was obtained. A left carotid angiogram showed no evidence of intracranial extension. Left frontal craniotomy was performed, and the left orbit was explored extra-

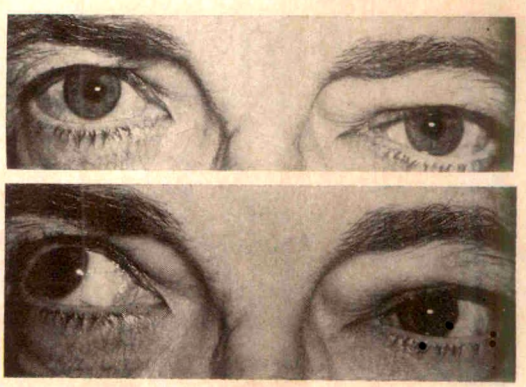


Fig. 1 (Guerry and Smith). Case 1. Top, Forward gaze; bottom, up and right gaze.

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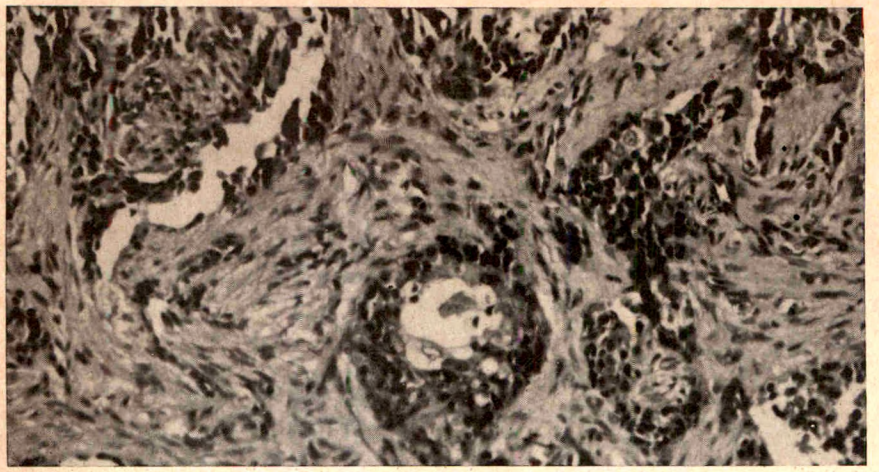


Fig. 2 (Guerry and Smith). Case 1. Histologic section (hematoxylin and eosin, ×440).

durally, revealing extensive tumor infiltration throughout the left frontal and ethmoid sinuses and the diploic space of the orbital roof. We attempted to excise as much of the tumor as possible, and she was then treated with radiotherapy.

Case 2—A 72-year-old man, first seen in January 1971, complained of swelling of the right brow and blepharoptosis of the upper eyelid. He gave a long history of sinus headaches and described intermittent soreness and swelling of the right brow for three to four years. Two weeks before examination he first noted blepharoptosis and consulted an otolaryngologist, who washed out his right antrum.



Fig. 3 (Guerry and Smith). Case 2. Top, Forward gaze; bottom, with eyes closed, note fullness over right brow.

He had mild adult onset diabetes. Otherwise his past history was unremarkable.

On Jan. 18, 1971, corrected visual acuity was 20/15 in both eyes. There was moderate blepharoptosis on the right (Fig. 3, top) with fullness over the right brow (Fig. 3, bottom). On palpation, a doughy area of resistance was felt under the superior lateral aspect of the orbital rim. Pupils, motility, slit-lamp examination, and dilated indirect ophthalmoscopy were unremarkable. Subtle hypesthesia in the first trigeminal division on the right was noted.

Skull and sinus x-ray films taken two months before were normal. These examinations were repeated, and again no abnormalities were seen. On Jan. 29, the right orbit was explored, and a typical frontal sinus mucocele was encountered. This was incised and drained, and tissue was sent for routine histologic examination. Examination of the biopsy material revealed well-differentiated squamous cell carcinoma infiltrating the wall of the mucocele.

Over the next two months he received 7,000 rads to the right orbit and supraorbital area. Initially he did well, but ten months later he returned with a recurrence of swelling over the right brow. He complained of pain and numbness in the first trigeminal division on the right side. On examination his visual acuity, fields, motility, and fundi were normal. Sinus x-ray films and tomograms of the right orbit showed a soft tissue mass in the inferolateral aspect of the right frontal sinus with extensive involvement of the sphenoid bone. On Dec. 8, he underwent radical surgical excision of his recurrent tumor that involved the orbit, frontal sinus, and the dura mater of the anterior fossa on the right side. The postoperative course was complicated, and he died Sept. 3, 1972. Autopsy was not performed.

Case 3—A 64-year-old man was first seen in 1964. On routine examination he had proptosis of

the left eye. He gave a history of chronic sinusitis and alcoholism. Sinus x-ray films showed evidence of chronic sinusitis and a typical left frontal sinus mucocele extending into the left orbit (Fig. 4). Review of x-ray films taken one year previously showed the mucocele present at that time.

The patient was not seen again until January 1966. In the interim there had been definite progression of the proptosis and repeat x-ray films showed enlargement of the mucocele. The left frontal sinus was explored surgically, and a large cystic tumor extended through a defect in the floor into the medial aspect of the left orbit. The nasofrontal duct was obliterated by tumor. Pathologic examination showed this to be squamous cell carcinoma. Postoperatively the patient did poorly, and he died of bilateral bronchopneumonia on the 24th day. An autopsy revealed extensive tumor involvement of the left frontal and ethmoid sinuses.

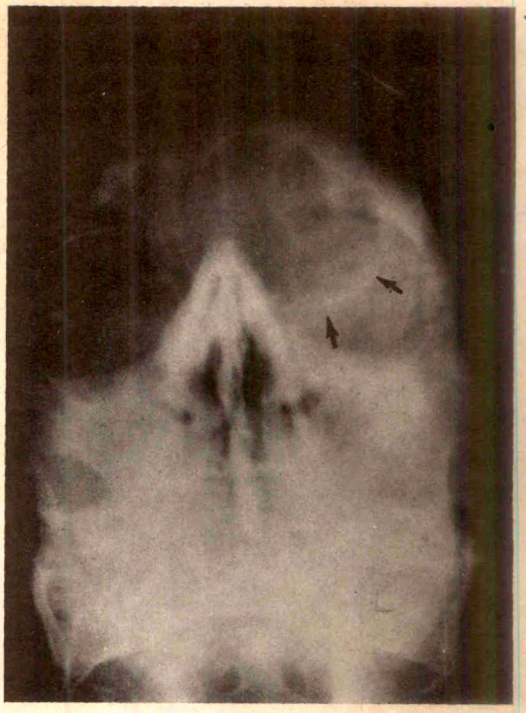


Fig. 4 (Guerry and Smith). Case 3. Arrows show leading edge of mucocele.

Discussion

In his 1921 Hunterian lecture, Howarth[2] defined mucocele as follows: "By the term mucocele of a sinus is meant the accumulation and retention within it of a mucous secretion owing to obstruction of its outlet with thinning and possible distention of one or more of the walls of the sinus." In the adult the sinus of origin is virtually always the frontal or ethmoid, the former occurring five times more frequently than the latter.[3] Often, the mucocele involves both sinuses, and its true origin cannot be determined. Mucoceles arising from the sphenoid and maxillary sinuses are extremely rare.

Howarth[2] emphasized the role of obstruction of the sinus ostium in the pathogenesis of mucocele. Bordley and Bosley,[4] in a recent review of 56 cases of frontal sinus mucocele, stated that obstruction of the nasofrontal duct was found at surgery in all 56 patients. While chronic inflammation, infection, anatomic variation, trauma, surgery, and tumor have been described as responsible for obstruction of the ostium, we are interested in the tumor. Lederer's[5] 1953 text is representative of the older literature in that it includes neoplasm in this list. Henderson's[6] excellent recent text on orbital tumors makes no mention of this point. The relationship between tumor and mucocele has been virtually forgotten. These three cases will serve to reemphasize this relationship.

In all three cases carcinoma of the paranasal sinuses was not suspected because the clinical and radiologic presentation was typical of a mucocele. There was unilateral blepharoptosis, proptosis with inferotemporal displacement of the globe, good visual acuity, diplopia (Case 1), and a history of chronic sinusitis. In Cases 1 and 3 where proptosis was present for at least seven and two years, respectively, the time course was misleading. However, squamous cell carcinoma in this area has a long and often asymptomatic course. It is possible, of course, that carcinoma was not responsible for the mucocele at all: rather, it occurred concomitant with the mucocele, both being related to chronic inflammation. Two patients (Cases 2 and 3) may have had cystic tumors rather than mucoceles. The point is, however, that tumor should always be suspected in this condition. Mere incision

and drainage without histologic verification are never sufficient in its management. The cause for obstruction of the sinus ostium should be determined.

Reese[7] found mucocele a common cause of unilateral proptosis when clinical and radiologic criteria were used to make the diagnosis. However, in his series of 877 consecutive cases of orbital neoplasms and simulating lesions studied histologically, there was not a single case of mucocele. He attributed this to the fact that "tissue from this lesion is never sent to the laboratory."[7] These cases demonstrate the need for careful pathologic examination.

Bone as well as soft tissue should be included in the specimen submitted. In the first case the one tumor-containing fragment had to undergo decalcification and was thus overlooked in the original pathologic report. While the ultimate outcome in this patient (Case 1) may not have been influenced by this error, the proper initial diagnosis could have spared her four subsequent operations.

The x-ray films in Cases 1 and 3 were textbook representations of frontal sinus mucocele. In Case 2, the x-ray films were completely normal, even on review. There are several lessons to be learned here. In this condition, tomography is essential, for the changes of a mucocele are often so subtle that the diagnosis cannot be made on x-ray films. More important, the presence of concomitant carcinoma cannot be ruled out on either tomography or x-ray films. One must first suspect its presence, obtain sufficient tissue at the time of surgery, and insist on careful histopathologic examination in all mucoceles.

Summary

Three patients presented with typical orbital mucoceles. However, subsequent histopathologic study revealed paranasal sinus concomitant squamous cell carcinoma in all three cases. Careful histologic investigation is necessary before considering orbital mucocele a benign process.

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METASTATIC CARCINOMA OF THE IRIS

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Metastatic carcinoma of the eye is a common sequela of widespread dissemination of malignancy.[1,2] Though the iris is a less common site of uveal involvement, metastases to the iris may occur and may produce a variety of clinical findings. We present the ocular findings, including anterior segment fluorescein angiograms, in four patients with metastases to the iris.

CASE REPORTS

Case 1—A 53-year-old white woman was admitted to the hospital on March 9, 1973, with a chief complaint of left eye pain and left arm weakness of two weeks' duration and left leg weakness of two days' duration. The patient had undergone a left radical mastectomy in August 1971, for anaplastic carcinoma. No lymph node involvement was found. In February 1973 the patient developed a recurrence of the tumor in the left chest wall and she received additional radiotherapy.

On admission, corrected visual acuity was 20/20 in each eye and intraocular pressure was 14 mm Hg in both eyes. Examination of the right eye was unremarkable. The conjunctiva showed mild hyperemia in the 9 o'clock position at the corneoscleral limbus in the left eye; the cornea was clear. There were two large gelatinous gray nodules on the iris in the 9 o'clock position (Fig. 1). One was near the pupil and the other extended into the angle and produced an extensive peripheral anterior synechia. The anterior chamber contained a mild aqueous flare and cellular response. Pupillary reaction in the left eye was absent in the area of the mass. No other abnormalities were noted in the left eye.

An iris fluorescein angiogram revealed two vascular tumors which fluoresced early (Fig. 2, top) and then produced late leakage of dye at the borders (Fig. 2, bottom).

A general physical examination revealed a 7 × 7-mm mass over the left occiput, enlarged lymph nodes in the left axilla, decreased motor strength, and deep tendon reflexes in the left upper extremity. Roentgenograms showed multiple nodules in both lung fields and lesions in ribs and spine.

Histopathologically, a biopsy specimen of the occiput mass revealed anaplastic adenocarcinoma. She refused further treatment and was discharged. She died at home two months later and an autopsy was refused.

Case 2—A 53-year-old white woman had been well until August 1972, when she was seen in the emergency room because of chills, abdominal pain, and cough productive of sputum. Chest and abdominal x-ray films were taken and the chest x-ray revealed a right pleural effusion with a mass lesion in the right upper lobe. Further evaluation in the hospital revealed sputum cytology suggestive of malignancy. Bronchoscopy showed pathologic findings in the right middle lobe and right lower lobe, and mediastinoscopy revealed an adenocarcinoma of the lung that was unresectable. The patient received a course of radiotherapy to the right chest and was discharged.

The patient was readmitted to the hospital in November 1973, with severe pain in the left eye of two days' duration. Visual acuity was R.E.: 20/20, and L.E.: 20/50; intraocular pressure was R.E.: 14 mm Hg, and L.E.: 40 mm Hg. In the left eye, the conjunctiva displayed intense hyperemia; the cornea showed microcystic edema centrally with small keratic precipitates on the endothelium; and the anterior chamber contained a moderate aqueous flare and cellular reaction. The left pupil was irregular and the iris displayed diffuse rubeosis iridis and areas of atrophy from 5:30 to 7 o'clock. White nodules were present on the anterior surface in-

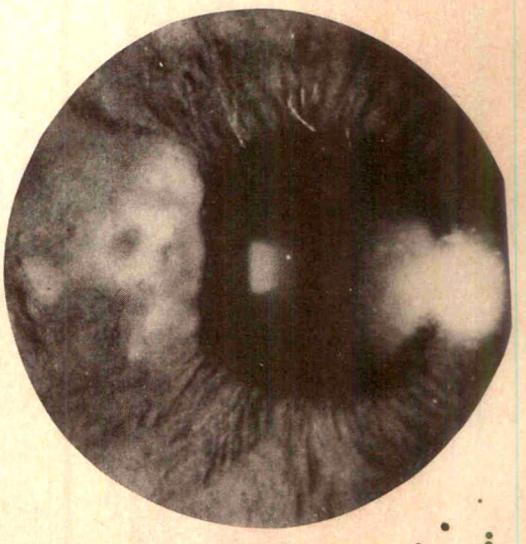


Fig. 1 (Freeman and Friedman). Case 1. Two large gelatinous nodules on the left iris at 9 o'clock. One nodule is at the pupillary border and the other extends into the angle.

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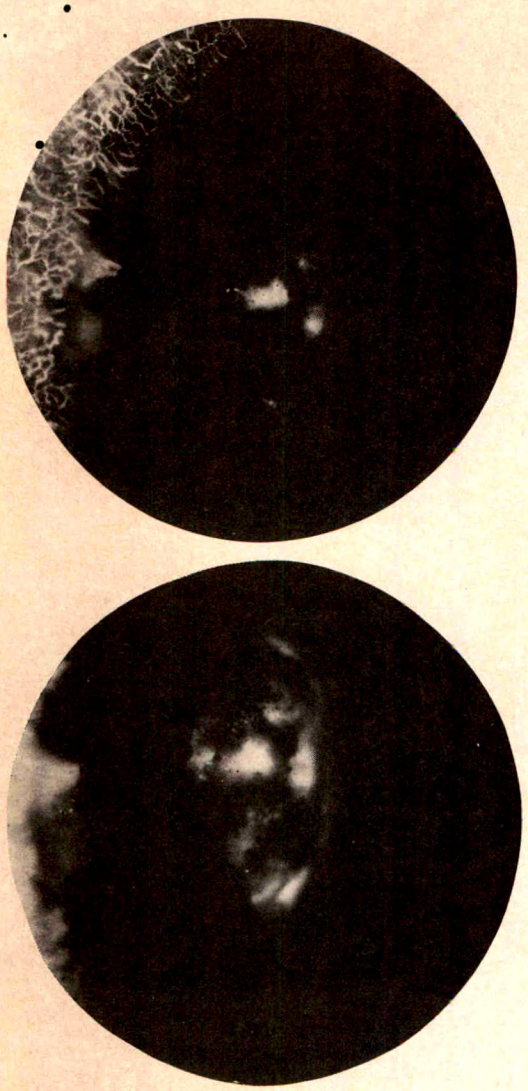


Fig. 2 (Freeman and Friedman). Case 1. An iris fluorescein angiogram revealing prominent fluorescence of the tumors in the early phase (top), and in the late phase leakage of dye (bottom).

feriorly and extended into the angle (Fig. 3).

A fluorescein angiogram of the iris revealed marked leakage of the fluorescein at the pupillary margin (Fig. 4). Near the root of the iris in the 6- to 8-o'clock position was an area of speckled fluorescence. A paracentesis was performed and cytologic examination revealed cells suggestive of malignancy.

Medical therapy was ineffective in controlling the glaucoma and the patient was treated with an injection of retrobulbar alcohol and radiotherapy. She died three months later and no autopsy was performed.

Case 3—A 54-year-old white woman was seen in the ophthalmology department because of a growth in the lateral angle of her left anterior chamber associated with marked photophobia and tearing. The patient had undergone a simple mastectomy six years before with no regional node removed and had manifested no evidence of any metastatic lesion since then.

Corrected visual acuity was 20/20 in both eyes; there was a slightly pink bulbar conjunctiva in the left eye with no dilated episcleral vessels locally; and the pupil was oval due to retraction temporally. A nodular, gelatinous mass was seen in the angle and posterior cornea extending from 1 to 4:30 o'clock with a large vessel coursing over it (Fig. 5). With the slit lamp the lesion readily transilluminated. The anterior chamber was clear. The fundi were unremarkable bilaterally. Intraocular pressure was R.E.: 14 mm Hg, and L.E.: 17 mm Hg.

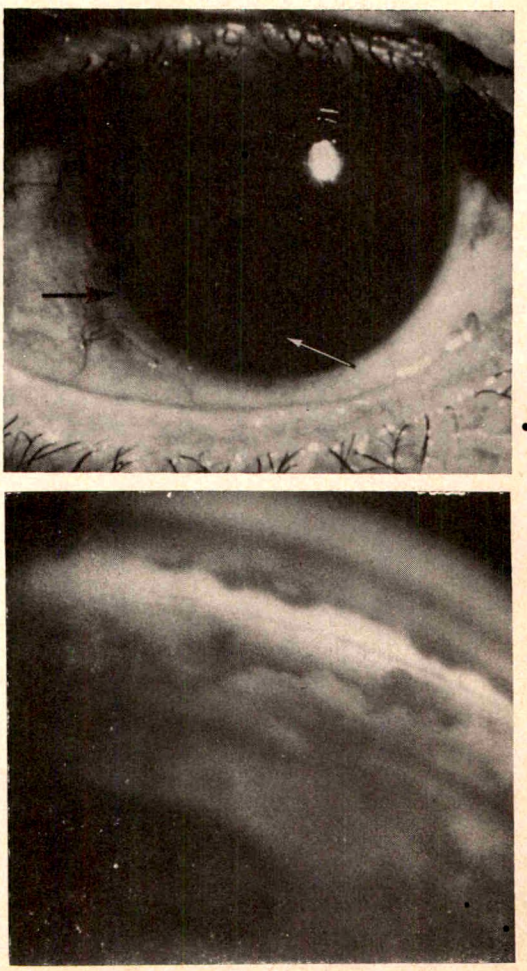


Fig. 3 (Freeman and Friedman). Case 2. Top, Multiple nodules present inferiorly on the iris surface, left eye (arrows). Bottom, Goniophotograph showing extensive infiltration of the angle by the tumor.

A biopsy specimen of the iris lesion and a diagnosis of metastatic anaplastic carcinoma was made (Fig. 6). The patient was lost to follow-up.

Case 4—A 41-year-old black man was seen in the eye clinic in August 1972, because of pain and redness in his right eye for two weeks. He was a former heroin addict who smoked two to three packs of cigarettes daily for about 25 years.

Corrected visual acuity was R.E.: 20/40, and L.E.: 20/20. Intraocular pressure was R.E.: 16 mm Hg, and L.E.: 18 mm Hg. The right conjunctiva showed moderate hyperemia; there were numerous tiny deposits on the corneal endothelium; and the anterior chamber displayed moderate aqueous flare and cells. At the pupil in the 10- to 11-o'clock position were two globular, translucent gelatinous white nodules (Fig. 7); the pupil reacted sluggishly. The remainder of the examination was within normal limits. A fluorescein angiogram revealed poor delineation of the tumor nodules. The central areas of the tumor nodules were dark during the early phase of the study although some leakage developed from the borders in the late phase (Fig. 8).

A chest x-ray film showed a left hilar mass and the patient was admitted to the hospital. Bronchoscopy revealed a left lower lobe infiltrate; a biopsy specimen showed an undifferentiated squamous cell carcinoma. Brain scan showed four separate lesions. The patient died two months later.

At autopsy, histopathologic examination of the right eye revealed a partially necrotic infiltrating, undifferentiated squamous cell carcinoma of the iris (Fig. 9).

Discussion

A recent study by Ferry and Font[2] indicated that metastatic carcinoma may well be the most common intraocular tumor based on their own study and data from several autopsy and clinical surveys.[1,3-5] In surveys of eyes removed at autopsy from patients who died from metastatic carcinoma, the incidence of ocular involvement has been reported by Bloch and Gartner[1] as 12% (28 cases in 230 patients) and by Guthert, Janisch, and Rossbach[3] as 0.5% (four cases in 853 patients).

In clinical studies of patients with known carcinoma, Godtfredsen[4] found six persons with ocular metastasis among 8,712 patients, most of whom were without known metastasis to another site, and Albert, Rubenstein, and Scheie[5] found five choroidal metastases among 213 patients known to have carcinoma with metastases.

Metastases to the iris may produce a variety of clinical findings, such as nodules on the iris or in the anterior chamber angle, anterior uveitis, rubeosis iridis, iris atrophy, hypopyon, hyphema, or secondary glaucoma.[6-10] Metastatic nodules on the iris or in the angle characteristically appear as grayish-white gelatinous lesions, frequently vascular, that tend to infiltrate the surrounding tissue.[7] In all our cases, tumor nodules

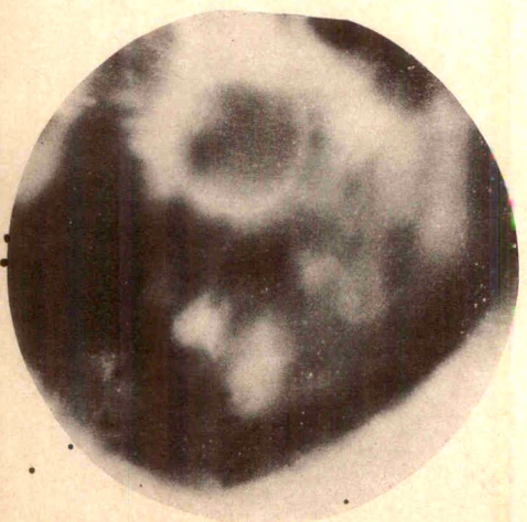


Fig. 4 (Freeman and Friedman). Case 2. Fluorescein angiography showing marked leakage of dye from new vessels on iris surface and area of speckled fluorescence inferiorly.

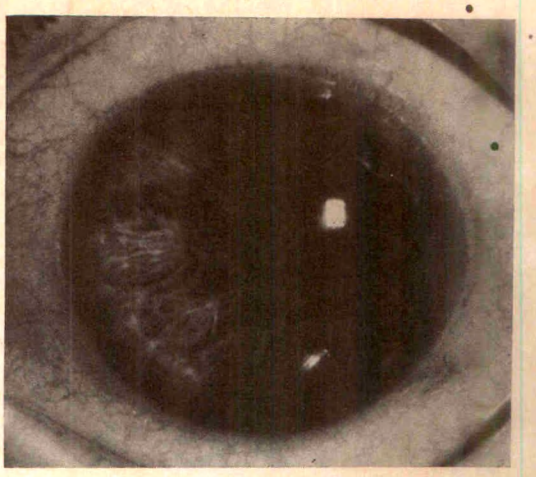


Fig. 5 (Freeman and Friedman). Case 3. An extensive gelatinous mass in the left eye, extending from 1 to 4:30 o'clock. Note temporal retraction of the pupil.

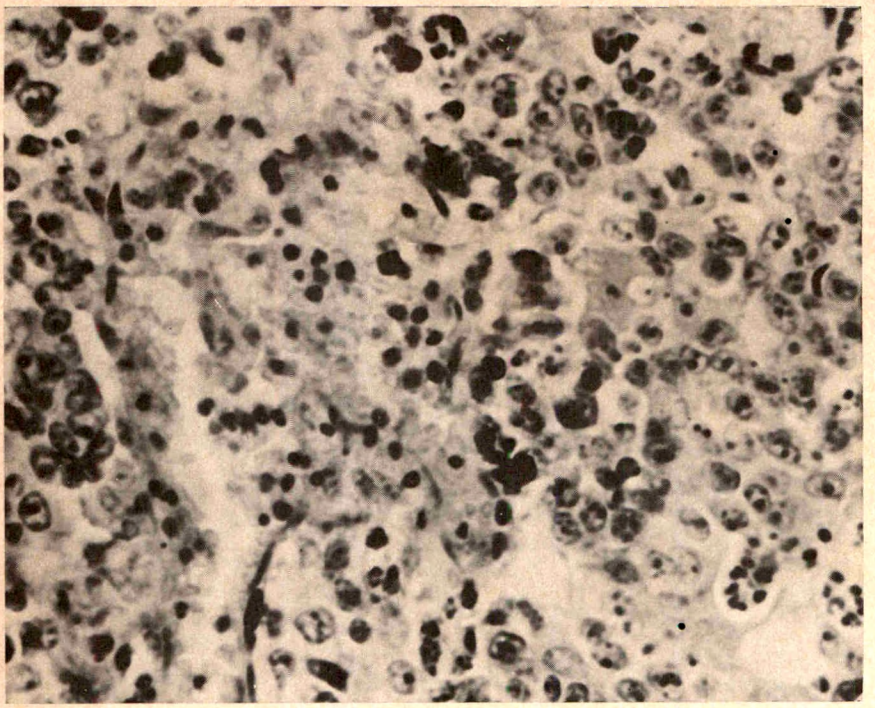


Fig. 6 (Freeman and Friedman). Case 3. Photomicrograph of the tumor reveals anaplastic carcinoma on the iris (hematoxylin-eosin, ×315).

showed the usual clinical appearance, a feature that makes the observer suspicious. As a consequence of their growth, iris metastases may produce pupillary abnormalities, as were noted in three patients (Cases 1, 2, and 4). In Case 2, iris atrophy developed as a probable sequela of anterior segment ischemia. The etiology of rubeosis iridis



Fig. 7 (Freeman and Friedman). Case 4. Two large globular, gelatinous nodules near the right pupil. (Disregard light reflexes at right.)

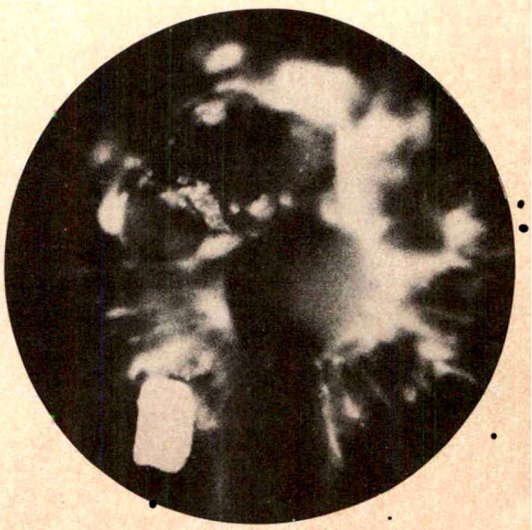


Fig. 8 (Freeman and Friedman). Case 4. Late phase showing leakage of dye from borders of tumor nodules.

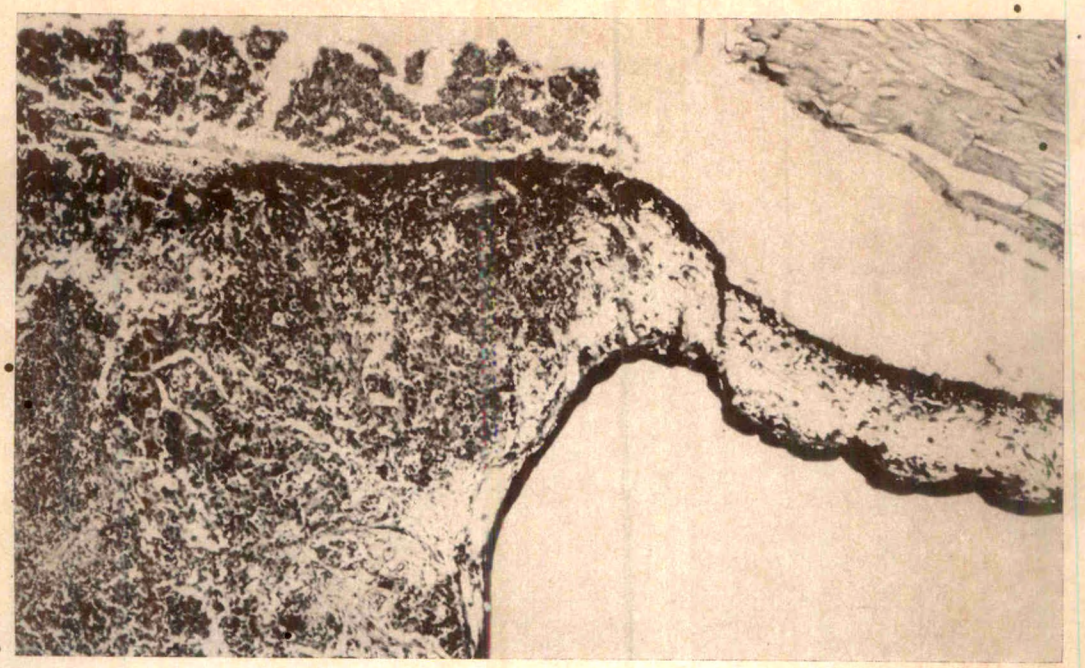


Fig. 9 (Freeman and Friedman). Case 4. Tumor is within iris stroma and on the anterior surface (hematoxylin-eosin, ×125).

may be either a result of anterior segment ischemia or secondary to a tumor angiogenic factor as described by Gimbrone and associates.[9] Their work suggests that iris neovascularization is stimulated either directly by a humoral factor from viable tumor cells or through an intermediary interaction with host tissues. As a result of some necrosis in the tumor, an inflammatory reaction was an almost constant feature in all our cases. An anterior uveitis so severe as to produce a hypopyon has been reported.[10-12] In one case, Levine and Williamson[10] noted the development of a hypopyon during the postoperative period after an uneventful intracapsular cataract extraction, mimicking an endophthalmitis. In Middleton's[12] case, paracentesis for diagnostic purposes resulted in extension of the tumor into the orbit. In Case 2, secondary glaucoma developed as a result of infiltration of the anterior chamber angle by tumor. Reese[13] also noted that a marked anterior uveitis may produce secondary glaucoma. Hyphema, though not seen in any of our patients, has been reported.[7]

Cheng, Bron, and Easty,[14] using fluorescein angiography, studied iris masses consisting of malignant melanomas, nevi, cysts, and vascular tumors, and observed that it was a useful technique for demonstrating vascular details not seen clinically. In most malignant melanomas, leakage of fluorescein into the tumor was observed. No leakage of dye was noted in any case of benign tumor. Similarly, metastatic tumors, as revealed by fluorescein angiography in our study, are more vascular than clinically apparent and leak dye during the study.

Summary

Of three women and one man with metastatic carcinoma of the iris, the average age of the four was 50.2 years. Two of the tumors originated in the breast and two in the lungs. The average survival from time of diagnosis of the iris lesion was less than six months. Each patient presented with

characteristic grayish-white translucent nodules on the iris or in the anterior chamber angle. The patients displayed other features of iris metastases such as secondary glaucoma, rubeosis iridis, iris atrophy, anterior uveitis, hypopyon, and hyphema. As an aid in the clinical evaluation, anterior segment fluorescein angiography was performed, revealing vascular details not seen clinically. Leakage of dye was a constant feature of the angiogram.

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NOTES, CASES, INSTRUMENTS

VISUAL EFFECTS OF PERIPHERAL AND SECTOR IRIDECTOMY

J. L. BUSTILLO, M.D.
Edmonton, Alberta

To determine any obvious clinical differences between peripheral and sector iridectomy, such as photophobia, I performed 50 uncomplicated intracapsular cataract extractions in 25 patients, one eye with peripheral iridectomy and the fellow eye with total iridectomy (Figure).

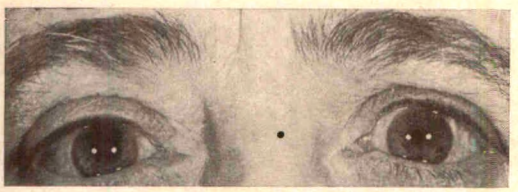


Figure (Bustillo). Patient with sector iridectomy (R.E.) and peripheral iridectomy (L.E.).

All patients were cooperative. Their average age was 69 years: the oldest was 85 and the youngest was 39. Five were fitted with contact lenses. They were followed from four months to two years. None were told about the particulars of the technique.

Visual acuities were expressed in decimal notation (Table). The mean visual acuity of the 25 eyes with peripheral iridectomy was 0.85 with standard deviation ±0.29. The mean visual acuity of the 25 eyes with sector iridectomy was 0.82 with standard deviation of ±0.28.

The differences between the two eyes for each patient were scaled according to the number of lines of difference on the visual acuity chart (Table). Student's *t*-test was applied to the resulting differences, including a correction for continuity.[1] Using this analysis the null hypothesis was accepted

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TABLE

RESULTS AND STATISTICAL CALCULATIONS

Case No.	Visual Acuity*		Lines of Difference,† Snellen
	Peripheral Iridectomy	Sector Iridectomy	
1	1	1	0
2	1	1	0
3	1	0.8	1
4	1	1	0
5	0.8	0.8	0
6	1.33	1.33	0
7	1	0.25	6
8	0.5	0.67	−1
9	0.33	0.33	0
10	1	1	0
11	0.5	0.5	0
12	1.33	1	1
13	0.8	0.8	0
14	0.8	0.8	0
15	0.8	0.8	0
16	1	1	0
17	0.5	1	−3
18	0.67	0.67	0
19	0.4	0.4	0
20	1	1	0
21	1.33	1.33	0
22	1	1	0
23	0.67	0.5	1
24	0.5	0.5	0
25	1	1	0

* Mean and standard error: peripheral iridectomy, 0.85 ± 0.29; sector iridectomy, 0.82 ± 0.28.

† Sum of lines difference, 5; Student's *t*-test = 0.113; $P > .50$.

($P > .50$), indicating no significant difference between the two eyes in this sample.

No patient reported any subjective difference between right and left eyes. While applying the ocular medications, relatives of two patients noticed that one of the pupils was not round.

SUMMARY

Twenty-five patients had bilateral cataract extractions: one eye with peripheral iridectomy and the fellow eye with sector iridectomy. They were followed from four months to two years. No significant differences in visual acuity between the two eyes were found. No patient reported any subjective difference between the right or left eye.

MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

NINTH PUPIL COLLOQUIUM

For 17 years a motley group of investigators has been getting together to compare notes on the pupil, their common area of academic interest. The group includes ophthalmologists, pharmacologists, psychologists, physiologists, neuroanatomists, neurologists, and bioengineers. The ninth meeting was held at the University of Iowa in Iowa City, May 30 and 31, 1975, and was hosted by the Department of Ophthalmology. Abstracts of the papers presented are as follows:

PUPILLARY RESPONSIVITY IN THE DETECTION OF DECEPTION PARADIGM

M. T. Bradley and M. P. Janisse (Winnipeg)

The pupils tend to be larger when the subject is sitting and thinking than when just sitting; but as a lie detector, the pupil is a failure.

DECREASED "AROUSAL DECREMENT" AS A FUNCTION OF SUBJECTS' EXPERIENCE WITH PUPILLOMETRIC EXPERIMENTS

P. E. Shrout, P. W. Beaver, and E. H. Hess (Chicago)

Many psychologists working with the pupil have noticed that subjects' pupils are biggest at the beginning of the experiment, and that one half hour later the pupils are significantly smaller, presumably due to the fact that the subjects are at first apprehensive, and later, bored.

PUPILLARY AND EVOKED POTENTIAL SIMILARITY IN MONOZYGOTIC TWINS AND SIBLINGS

F. Bock, S. Steinhauer, and G. Hakerem (New York)

Pupillary dilation and cortical evoked responses were recorded from 19 pairs of twin (ten monozygotic, nine dizygotic) and from eight sibling pairs. The monozygotic twin pairs were more alike on their responses than were other pairs. It was then suggested that it was unwise in pupillary experiments to average across different subjects, because each subject's psychosensory pupillary dilation is reproducible, and as characteristic for that subject as his fingerprint.

A COMPREHENSIVE, COMPUTER-SIMULATED MODEL OF THE PUPIL LIGHT REFLEX

J. L. Semmlow (Chicago)

Known pupillary behavior in various situations is translated into mathematical and electronic terms and then reconstructed into a computer program. When the computer is then given "light stimuli" of various kinds it will produce and record "pupillary responses" of remarkable similarity to the real thing. This technique is now good enough for "pilot studies" of physiologic pupillary experiments to be first run on the computer.

OBJECTIVE PUPILLOMETRIC PERIMETRY

K. Sugita (Nagoya)

In a film presentation of a new instrument, the pupil was observed in darkness inside a bowl perimeter via infrared television. Spots of light of increasing size or intensity were presented at a given locus in the field, until the operator, watching his TV monitor, could see the pupil move. A visual field could thus be plotted and compared with conventional perimetry.

SURGICAL TREATMENT OF PATIENTS WITH IMPAIRED NEAR REFLEX

S. Shimizu, S. Narasaki, and R. Ashikawa (Tokyo)

Accommodation, convergence, and pupillary near reaction were apparently improved

after trigeminal ganglion block, and, in patients with sinusitis, after draining the sphenoid sinus.

Recent Technical Advances in Pupillometry

D. Sheena (Waltham, Mass.)

Some refinements have been added to the only binocular electronic pupillometer now being made and marketed in this country.

Influence of Tricyclic Antidepressants on the Miotic Action of Guanethidine and Thymoxamine

P. Turner (London)

Tricyclic antidepressant drugs inhibit the uptake of guanethidine into peripheral adrenergic neurones and block its antihypertensive action. Studies were carried out to determine if their oral administration reduced the miotic effect of topically applied guanethidine. It appeared that this was so, but subsequent studies showed that the miotic effect of thymoxamine, an α-receptor blocking drug, was also reduced. It was concluded, therefore, that some other pharmacological mechanism, such as anticholinergic activity, was responsible for this effect.

Analysis of Muscarinic Transmission in the Superior Cervical and Ciliary Ganglion of the Cat

M. C. Koss and J. A. Rieger (Oklahoma City)

Pupil size and postganglionic ciliary nerve activity were recorded in anesthetized cats. Hexamethonium blocked the ciliary ganglion completely. Postganglionic activity was abolished and was not reversed by increasing the stimulus frequency or by administration of physostigmine. DMPP (a nicotinic agonist) activated the ciliary ganglion but McN-A-343 (a muscarinic agonist) failed to stimulate the ganglion. These results indicate that, unlike sympathetic ganglia, transmission in the ciliary ganglion does not take place by means of a muscarinic (atropine sensitive) mechanism.

Cholinergic Supersensitivity in Adie's Syndrome: Pilocarpine vs. Mecholyl

S. F. J. Pilley and H. S. Thompson (Iowa City)

Documented Mecholyl tests (2.5%) were performed on 57 unilateral Adie's pupils between 1968 and 1975. In only 36 of these (63%) did the Adie's pupil demonstrate supersensitivity by constricting significantly more than the unaffected pupil during the 30-minute test period. Of these patients 27 were tested both with Mecholyl (2.5%) and with pilocarpine (0.125%) between 1971 and 1975. (Some of these patients were selected for pilocarpine testing because Mecholyl had failed to demonstrate supersensitivity of the Adie's pupil.) Mecholyl demonstrated supersensitivity in 54%. Pilocarpine demonstrated supersensitivity in 69% and induced a greater anisocoria than did Mecholyl. It was concluded that the amount of supersensitivity of the denervated sphincter in Adie's syndrome is highly variable, that 2.5% Mecholyl is so weak a solution it will constrict only the most sensitive of Adie's pupils, and that pilocarpine (0.125%) is an adequate substitute for Mecholyl 2.5% when testing for cholinergic supersensitivity in Adie's syndrome. Because of its stronger miotic action pilocarpine 0.125% is in some ways a preferable drug: (1) supersensitivity is demonstrable in a higher proportion of Adie's patients, (2) it produces a greater and thus more visible degree of anisocoria, and (3) a negative test is more valid.

Pupillary Abnormalities in Charcot-Marie-Tooth Disease

J. L. Keltner (New Haven)

A single family with dominantly inherited Charcot-Marie-Tooth disease was examined.

Fifteen members had the disease, and of these 13 had large poorly reactive pupils strongly resembling Adie's pupils.

The Latent Period of the Pupillary Light Reaction

G. Cibis (Iowa City)
E. Campos and E. Aulhorn (Tübingen)

The pupillomotor latent period was determined beginning at threshold and going to the fastest possible response. Different target sizes and different retinal locations were used. The results indicated that the pupillomotor latent period for a given stimulus is a function of pupillomotor threshold of that stimulus.

Drug Testing in Horner's Syndrome

B. Grimson and H. S. Thompson (Iowa City)

A large series of patients with Horner's syndrome was reviewed, and the following points were made: (1) Cocaine does not help to localize the lesion, because any pupil with Horner's syndrome dilates poorly to cocaine. (2) Postganglionic lesions can be recognized by their failure to dilate to hydroxyamphetamine (Paredrine). (3) Horner's syndrome of the head (postganglionic) is often benign, but of the chest or neck (preganglionic) is frequently associated with malignancy.

The Fluctuating Anisocoria of Horner's Syndrome

S. F. J. Pilley and H. S. Thompson (Iowa City)

The characteristic transient increase in anisocoria in Horner's syndrome after the lights go out was compared with "central" or "physiological" anisocoria. Polaroid flash photographs taken at 4 to 5 seconds of darkness and 10 to 12 seconds of darkness are helpful in quickly confirming the diagnosis of Horner's syndrome in cases of unexplained anisocoria.

Pupillary and Iris Anomalies in Multiple Lentigenes (Leopard) Syndrome

R. Zahoruk, D. Rosenthal, and J. Gowing (Hamilton, Ontario)

A case of this syndrome was demonstrated: many unusually dark freckles (lentigenes), electrocardiogram defects, hypertelorism, pulmonary stenosis, abnormalities of genitalia, mental and growth retardation, and sensorineural deafness. This patient also had what appeared to be a coalescence of iris freckles inferiorly in one eye with shrinking of the iris, distortion of the pupil, and ectropion uveae.

Wernicke's Hemianopic Pupillary Phenomenon in Supragenicular Lesions

G. Cibis (Iowa City)
E. Campos and E. Aulhorn (Tübingen)

The pupillomotor threshold was determined perimetrically in blind and seeing areas of the same eye in patients with homonymous field loss due to lesions above the lateral geniculate. The results support the contention that Wernicke's pupillary hemiakinesia can be demonstrated in any homonymous field loss by pupillomotor threshold determination.

Oculomotor Paresis with Cyclic Spasms

I. E. Loewenfeld (Detroit)
H. S. Thompson (Iowa City)

Oculomotor paresis with cyclic spasms is a rare syndrome, usually noticeable at birth or developing during the first year of life. Typically there is unilateral blepharoptosis, with mydriasis, limitation of extraocular movements, and accommodative loss. Amblyopia is common, but there are no other constantly associated ocular or neurologic defects. On this background of third nerve paresis, spastic movements occur at regular intervals: once every two minutes or so the

drooping eyelid will be raised, the globe will wander toward midline, the pupil will contract and accommodation increase. These spasms will last about 10 to 30 seconds and then give way again to the paretic phase. The cyclic movements persist unchanged for many years, as far as is known throughout the patient's lifetime. They continue even during sleep, though at a reduced rate and amplitude, and subside only in deep narcosis.

Since this phenomenon was first described, opinions have been divided about its mechanism and about the location and the nature of the responsible defect. There were two main trends of thought: one placing the lesion in the oculomotor nucleus, the other postulating an intracranial third nerve defect.

We believe that these two kinds of oculomotor damage are not mutually exclusive. On the contrary, a third nerve injury, caused at birth or in early childhood by trauma or infectious disease, must bring about retrograde degeneration of the oculomotor neurons, so the lesion involves not only the efferent third nerve fibers, but also injures the nucleus. Furthermore, such early retrograde nuclear damage is likely to interfere with the establishment of proper synaptic contacts between the oculomotor neurons and their supranuclear connections, and this could explain the mechanism of the intermittent spasms.

H. STANLEY THOMPSON

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Published monthly by the Ophthalmic Publishing Company
233 East Ontario St., Chicago, Illinois 60611

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AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY 1975

The 80th Annual Meeting of the American Academy of Ophthalmology and Otolaryngology was one of the most successful from many points of view. As this report is written on the third morning of the meeting there were already more ophthalmologists registered than have attended any meeting of the Academy except that in Las Vegas four years ago. Unaudited figures show a total attendance of 10,014, including 4,630 ophthalmologists; 1,990 otolaryngologists; 1,787 technical exhibitors; and 1,607 at the ladies registration. Additionally, there were at least 1,289 full-members at the business meeting (this is the number of ballots cast), which made this the largest attended business meeting in Academy history.

The scientific program was outstanding and the arena was at all times well filled as were the many adjacent rooms in which special programs were being conducted. A drug symposium on Sunday before the opening of the regular session nearly filled the Grand Ballroom of the Statler-Hilton Hotel. Simultaneously there was standing room only at the National Society for the Prevention of Blindness conference at the Sheraton-Dallas.

The scientific program was opened by the president, Frank W. Newell, with the presentation of honor awards. The annual award for a lay person was given to Mr. George Werntz, Jr., the retired executive vice-president of Seeing Eye, Inc. Under Mr. Werntz's guidance, Seeing Eye made great contributions to ophthalmology by support grants for construction and research. A second award to a lay person was given to Miss Gladys Thompson, the retired Academy headquarters office administrator. Miss Thompson managed the affairs of the Academy efficiently and loyally for some 24 years, and the award was a small token of the affection and gratitude that each of us in Academy

administration have for Miss Thompson.

Dr. Newell's presidential speech addressed itself to continuing education of the physician and to the challenge presented by a rapidly increasing number of ophthalmologists. Dr. Newell estimated that there can be some 20,000 ophthalmologists by 1990, who would provide medical eye care for our entire populace.

The guest of honor, Irving H. Leopold, spoke on new dimensions in ocular pharmacology and emphasized that ophthalmologists must be familiar with only a few drugs but that they must know in intimate detail the actions, side effects, and interactions of this small number. The XXXII Edward Jackson Memorial Lecture was given by Frederick C. Blodi. This was a superbly illustrated lecture, "The Pathology of Orbital Bones." The remainder of the morning was also devoted to the orbit with emphasis on computerized tomography. A particularly interesting paper was given by Hilal, Trokel, and Coleman, showing the kinds of detail that can be obtained by modifications of the standard EMI axial tomography instrument. This instrument combined with ultrasonography suggests the obsolescence of invasive contrast studies for diagnosis of orbital disease. One of the nonorbital papers was an outstanding presentation by Mittelman and Folk on the evaluation and treatment of superior oblique palsy.

On Tuesday morning the first of the parallel sessions began. A program on oculoplastic complications—prevention and treatment—was given in the theater while the regular scientific program continued in the arena. The excellence of both programs was underscored by the capacity attendance. The highlight of the arena program was a symposium on the optic disk and glaucoma with most informative papers by Paul Henkind, Sohan Hayreh, Peter Kronfeld, George Spaeth, and Stephen Drance. Bernard Schwartz moderated the symposium and the panel concluded that no one technique adequately evaluated the optic disk but that stereoscopic photography was probably the best method of recording change. However, even more important was careful examination of visual fields, since Dr. Drance showed that field changes can occur before ophthalmoscopically visible optic disk changes. Although mechanical pressure may interfere with axoplasmic flow and produce a field defect the most convincing evidence still appears to be that of the "vascular school" which indicates that interference with the blood supply from the short posterior ciliary arteries to the disk causes a loss of neuronal and glial tissue.

The exhibits this year were superb. The first prize was awarded to the exhibit "The Invisible Eye Patch" by Harold P. Kolker and Anthony R. Caputo which described the use of convex 17-diopter lenses for obstructing the vision in the better eye in amblyopic children. The second prize went to "The Diabetic Retinopathy Study," under the aegis of the National Eye Institute. The exhibit was put together by Matthew Davis and Fred Ederer; the third prize went to a group from the Bascom Palmer Eye Institute on "Fungal Keratitis—Diagnosis, Treatment, and Research," by Richard K. Forster, Gerbert C. Rebell, and Fernando G. Gonzalez. I will take a reporter's prerogative to add that my own choice for best exhibit was Norman Byer's "The Peripheral Retina in Profile," which was truly a tour-de-force of photography and teaching.

There were spirited contests for several offices, which generated unusual interest in the election. Bradley R. Straatsma received some 77% of the ballots cast for president-elect. Other officers for 1976 are: John F. Daly, president; Marshall Parks, first vice-president; Jack R. Anderson, second vice-president; and P. Robb McDonald, third vice-president. Burton J. Soberoff was named councillor. C. M. Kos was renamed secretary-treasurer. Frederick C. Blodi, David Shoch, and Bruce E. Spivey were renamed to the ophthalmic secretariat.

Next year's meeting will take place in Las Vegas Oct. 6-10. Mark your calendars.

DAVID SHOCH

CONTINUING MEDICAL EDUCATION

Since the publication of the Coggeshall Report (Planning for Medical Progress through Education: A report submitted to the Executive Council of the Association of the American Medical Colleges, Evanston, Illinois, Association of the American Medical Colleges, 1965), American medical education has been the topic of a variety of reports. The 1973, "Evaluation in the continuum of medical education: Report of the Committee on Goals and Priorities of the National Board of Medical Examiners," summarized the changes in an exemplary manner. The committee was chaired by William D. Mayer, dean and director of the University of Missouri-Columbia School of Medicine. Committee members included two internists, a surgeon, a pediatrician, a psychiatrist, and a biochemist. The remaining members included the president of the University of Toronto, the director of research and medical education at Southern California, the dean for medical education at Southern Illinois College of Medicine, a vice-president of the Robert Wood Johnson Foundation, and the director of the Department of Academic Affairs of the Association of American Medical Colleges.

The Coggeshall Report signally increased the political influence and activities of the Association of American Medical Colleges. Earlier, the Association was a small group, known within and without as "The Deans' Club," and dealt mainly with technical problems of medical education. Today in addition to medical school executives the association includes a teaching hospital council and a council of academic societies. The annual meeting is an exciting educational event.

The headquarters is now in Washington, D.C., and, under the dynamic and creative leadership of Dr. John A. D. Cooper, the Association plays a major role in medical decision-making in the Federal government. The members adopted the keystone of their policy in 1971:

> The Association of American Medical Colleges endorses the concept that graduate medical education ultimately should become the responsibility of academic medical centers. Through this endorsement the Association urges the faculties of academic medical centers to develop in conjunction with their parent universities and their teaching hospitals programmatic plans for taking responsibility for graduate medical education in a manner analogous to presently established procedures for undergraduate medical education.
>
> Assumption of this responsibility by academic medical center faculties means that the entire faculty will establish mechanisms to: determine the general objectives and goals of its graduate programs and the nature of their teaching environment; review curricula and instructional plans for each specific program; arrange for evaluating graduate student programs periodically; and confirm student readiness to sit for examinations by appropriate specialty boards.
>
> The Association encourages hospitals with extensive, multiple graduate education programs which are not now affiliated with academic medical centers to develop their own internal procedures for student selection, specific program review, and proficiency examinations. The accrediting agency is urged initially to accredit the entire graduate program of these hospitals. Ultimately, these institutions should either develop affiliations with degree-granting academic medical centers or seek academic recognition as freestanding graduate medical schools.
>
> The Association further urges that the specialty boards continue to develop test instruments for measuring achievement of individual candidates that avoid superimposing rigid program requirements on the academic medical centers.
>
> It is essential that all related components (including hospitals) of academic medical centers jointly develop appropriate financing for the program costs of graduate medical education.

The Coggeshall Report was followed by the 1966 report concerning graduate medical education prepared by a committee headed by J. S. Millis, president of Western Reserve University. ("The graduate education of physicians. Report of citizen committee on graduate medical education.") This commission emphasized four major trends: (1) increasing knowledge and resulting increase in specialization; (2) rising expectation and demands for medical and health care; (3) changing geographic distribution of the population; and (4) increasing institutionalization of medical practice.

The Millis Report triggered many changes in medical education: elimination of the rotating internship that was followed by nearly total elimination of the internship itself, a restructured fourth year of medical school education, recognition of the American Board of Family Practice, and the establishment of graduate training programs.

The Commission prompted the formation of a new organization, the Commission of Graduate Medical Education, for the purpose of planning, coordinating, and periodically reviewing the standards for graduate medical education. They proposed that the best method for securing a board of outstanding caliber would be to have the members appointed by the American Medical Association Council on Medical Education. This was not to be. The committee evolved is called Liaison Committee on Graduate Medical Education and institutional members represent the American Board of Medical Specialities, the American Hospital Association, American Medical Association, Association of American Medical Colleges, and the Council of Medical Speciality Societies.

In all, the National Board of Medical Examiners has been playing an increasingly dominant role. The testing business is a large one with the Educational Testing services at Princeton, New Jersey; the Council on Academic Testing; Science Research Associates; and others playing an important role. Standing in the background waiting for a role to develop are the major computer industries. The National Board of Medical Examiners has emerged as the main group in the testing of physicians. Originally, this involved the testing of medical students with the third and final examination permitting licensure without further testing in many states. Now the National Board of Medical Examiners provides the testing for foreign medical graduates (EFMNG), the FLEX examination for state licensure, some speciality board examinations as well as self-assessment examinations, and most recently examinations for professional assistants.

Paralleling the emphasis of the National Board in the examination and certification process is a completely opposite tendency in which medical schools are discontinuing grading and providing solely pass-fail scores. This is not popular with the current generation of medical students and several schools are returning to grading. The emphasis on state medical boards and licensure, however, is being de-emphasized and particularly foreign medical graduates and those working in state institutions may avoid the formal requirements of licensure. Relicensure is becoming popular with state legislatures, but each legislature plans to do this through evidence of graduate education and not by examination.

Several boards now provide the same examination to their residents in training as to the candidates for the final certification. Curiously, some candidates do as well in their first few months of training as other candidates do after three and four years of training. Thus, no one suggests that the examination process is so sensitive as to permit certification only on the basis of an examination without reference to completion of training program.

Those involved in the examination process recognize many weaknesses. Candidates from some institutions never fail the written examinations. Candidates in the upper percentile of the written examination usually do well in subsequent oral examination. The major problem arises with candidates who just scrape through a written test. This group includes those whose educational credentials are weak, but often also individuals for whom English is not the primary language. Those interested in test construction wonder if indeed they are testing the educational aspect or the applicant's knowledge of English.

Underlying the entire test procedure is the awareness that experts in educational testing do not agree with some of the basic premises of testing in medical education. All agree that one can measure cognitive ability

—one can take a book, scramble the facts, and learn if the student can answer questions correctly. The disagreement comes in whether one can take similar facts and make them a test in problem solving, clinical skill, attitude, wisdom, or judgment. These are interesting questions, and those concerned with the trends of medical education will find this report of the Committee on Goals and Priorities of the National Board of Medical Examiners a worthwhile presentation of current medical developments.

FRANK W. NEWELL

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper; with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

VAN DONGEN'S "OLD CLOWN" AND HIS OPHTHALMIC PROBLEMS

Editor:

While visiting the Geneve Petit Palais exposition, "From Impressionism to Picasso," I was struck by the Van Dongen painting "The Old Clown." This painting is a psychological study of an aging clown pathetically trying to give the impression that he is still funny. The wrinkled, ravaged face and tired, drooping hands contrast sharply with his clown costume and bright red hair, strengthening even further the impression of old age. Van Dongen, who was quite young when he did this painting, intuitively expresses all the deep human loneliness and tragedy accumulated in aging old men.

The strong artistic impression this portrait made on me did not prevent my looking at it through professional eyes and noting the ophthalmological interest it presented. If we assume that the clown is looking to the left, then the left eye remains in the middle; the left palpebral phanta is a little wider and it may be that it was a Duane syndrome that Van Dongen observed. If our patient—the old clown—is looking straight ahead with his left eye, which in my opinion seems more plausible, then he has a right strabismus convergens concomitans or a strabismus paralyticum due to right rectus externus palsy. In the latter case the old clown sees us double from his frame!



Figure (Manor). Van Dongen's "Old Clown."

R. S. MANOR, M.D.
Petah Tikva, Israel

BOOK REVIEWS

ADLER'S PHYSIOLOGY OF THE EYE, 6th ed. CLINICAL APPLICATION. Edited by Robert A. Moses. St. Louis, C. V. Mosby, 1975. Clothbound, 702 pages, table of contents, index, 624 black and white figures. $27.50

In 1970 Dr. Moses presented the world of ophthalmology with the fifth edition of Adler's Textbook of Physiology. To succeed in the tradition and standards of Francis Heed Adler was no commonplace effort. Now the sixth edition has appeared, which promises to be as well received as its precedent edition. In serving as editor, Dr. Moses himself has developed and written at least a half dozen chapters on several subjects in visual physiology, and, in addition, solicited and received the help of a dozen authors who have placed their specific expertise under his editorship. Commendably, these experts have

been chosen from basic fields of science as well as from ophthalmology. In this edition there are also 23 chapters. No extensive revision in format has been made. The chapters on retinal physiology and chemistry have been rearranged to accommodate new and recent information. A separate short chapter (Chapter 4) on mechanism of sensation has been added.

The result of Dr. Moses' energy is an erudite and useful text for students, residents, and practitioners who wish to place clinical judgment on a foundation of acceptable and current knowledge of how the eye works. We again congratulate Dr. Moses and recommend the sixth edition of Adler for the library of just about everyone interested in ophthalmology and visual science.

MARVIN L. SEARS

OCULAR MANIFESTATIONS OF INBORN ERRORS OF CARBOHYDRATE AND LIPID METABOLISM. By Jules François. Basel, Switzerland, S. Karger, 1975. Paperbound, 175 pages, table of contents, index, 1 table, 85 black and white figures. $32.50

The discussion of inborn errors of carbohydrate metabolism includes transferase and kinase types of galactosemia, von Gierke's disease and Pompe's disease. The role of glucose-6-phosphate dehydrogenase deficiency as a cause of cataract or ocular neuropathy is briefly considered.

The major portion of the discussion concerns a variety of disorders of sphingolipid metabolism. Additionally, there is a discussion of neutral lipidoses, Refsum's disease, familial lipoprotein deficiencies, and the primary hyperlipoproteinemias. The volume concludes with a discussion of the mucolipidoses.

Once again, as with all of François's work, one is impressed with his remarkable energy, comprehensive survey of prior work, and his logical synthesis of disease entities.

FRANK W. NEWELL

THE PERCEPTION OF LIGHT AND COLOUR. By C. A. Padgham and J. E. Saunders. Academic Press, Inc., 1975. Clothbound, 192 pages, index, 3 black and white figures, 7 color plates. $16.50

This volume is an introductory text intended for advanced high school and first year university students with some knowledge of physics. It offers a brief survey of the functional aspects of light perception and a somewhat more detailed description of the mechanism of color vision. Certain practical problems concerning the production of color and the measurement of color from the point of view of color specification are covered. The book contains a great deal of information organized in a usable way.

My major criticism of the book concerns the lack of references with regard to the origin of the ideas and data presented. Although the book is intended to be a general introduction to the subject of light and color, I do not think that documentation of the origin of the more than 100 figures in the book would confuse or distract the reader. Adequate but not excessive citation would allow the interested reader to pursue primary literature in a specific area more easily.

In summary, this is a useful book to recommend to a science-oriented student or layman who wishes to get a feeling for how we see light and color.

JOEL POKORNY

LES CONJONCTIVITES À VIRUS. By G. Coscas and R. Nataf. Paris, Masson et Cie, 1975. Clothbound, 96 pages, table of contents, index, 42 black and white figures, 11 color plates. $31.53

This is one of a series of monographs published under the guidance of the Societe Francaise d'Ophtalmologie. The scope of this text is limited strictly to viral disease of the conjunctiva and does not describe those diseases due to chlamydial agent or herpes dis-

ease of the cornea. It it a short, easily read well-illustrated book presented at the level of the ophthalmologist with special interest in external disease.

The first chapter is an introduction to virology. Subsequent chapters proceed in a methodologic manner, covering the clinical manifestations, epidemiology, morphology, pathogenesis, and treatment for each of the viral diseases. The virology is generally up-to-date and includes excellent sections on the adenoviruses, molluscum, and verruca, acute hemorrhagic conjunctivitis, the myxoviruses, paramyxoviruses, and arboviruses. The discussions certainly reflect the continental tradition for precise descriptions of clinical entities.

Therapeutics is discussed briefly and for the most part differs from the current state of the art in North America. Undue attention is paid to therapy with gamma globulins, interferons, vaccines, and antiseptics.

On the basis of completeness of clinical descriptions and excellent illustrations, this book will find a welcome place in most libraries. Sufficient English captions and summaries make this text of general interest.

MARK B. ABELSON

SYMPOSIA

STUDIES ON EXCITATION AND INHIBITION IN THE RETINA. Edited by Floyd Ratlif. New York, Rockefeller University Press, 1974. Clothbound, 688 pages, table of contents, index, 274 black and white figures. $22

H. K. HARTLINE AND C. H. GRAHAM: **Nerve impulses from single receptors in the eye**

C. H. GRAHAM AND H. K. HARTLINE: **The response of single visual sense cells to lights of different wave lengths**

H. K. HARTLINE: **Intensity and duration in the excitation of single photoreceptor units**

H. K. HARTLINE AND P. ROBB MCDONALD: **Light and dark adaptation of single photoreceptor elements in the eye of *Limulus***

H. K. HARTLINE, LORUS J. MILNE, AND I. H. WAGMAN: **Fluctuation of response of single visual sense cells**

H. K. HARTLINE, HENRY G. WAGNER, AND E. F. MACNICHOL, JR.: **The peripheral origin of nervous activity in the visual system**

F. A. DODGE, JR., B. W. KNIGHT, AND J. TOYODA: **Voltage noise in *Limulus* visual cells**

FLOYD RATLIFF, H. K. HARTLINE, AND DAVID LANGE: **Variability of interspike intervals in optic nerve fibers of *Limulus*: effect of light and dark adaptation**

H. K. HARTLINE: **The response of single optic nerve fibers of the vertebrate eye to illumination of the retina**

H. K. HARTLINE: **The receptive fields of optic nerve fibers**

H. K. HARTLINE: **The effect of spatial summation in the retina on the excitation of the fibers of the optic nerve**

H. K. HARTLINE: **The neural mechanisms of vision**

H. K. HARTLINE: **The discharge of impulses in the optic nerve of *Pecten* in response to illumination of the eye**

H. K. HARTLINE: **Inhibition of activity of visual receptors by illumination of nearby retinal areas in the *Limulus* eye**

H. K. HARTLINE, HENRY G. WAGNER, AND FLOYD RATLIFF: **Inhibition in the eye of *Limulus***

H. K. HARTLINE AND FLOYD RATLIFF: **Inhibitory interaction of receptor units in the eye of *Limulus***

H. K. HARTLINE AND FLOYD RATLIFF: **Spatial summation of inhibitory influence in the eye of *Limulus*, and the mutual interaction of receptor units**

FLOYD RATLIFF AND H. K. HARTLINE: **The responses of *Limulus* optic nerve fibers to patterns of illumination on the receptor mosaic**

TSUNEO TOMITA: **Mechanisms of lateral inhibition in the eye of *Limulus***

RICHARD L. PURPLE AND FREDERICK A. DODGE: **Interaction of excitation and inhibition in the eccentric cell in the eye of *Limulus***

H. K. HARTLINE, FLOYD RATLIFF, AND WILLIAM H. MILLER: **Inhibitory interaction in the retina and its significance in vision**

FLOYD RATLIFF, H. K. HARTLINE, AND WILLIAM H. MILLER: **Spatial and temporal aspects of retinal inhibitory interaction**

DAVID LANGE, H. K. HARTLINE, AND FLOYD RATLIFF: **Inhibitory interaction in the retina: techniques of experimental and theoretical analysis**

FLOYD RATLIFF, H. K. HARTLINE, AND D. LANGE: **The dynamics of lateral inhibition in the compound eye of *Limulus***

D. LANGE, H. K. HARTLINE, AND F. RATLIFF: **The dynamics of lateral inhibition in the compound eye of *Limulus***

FLOYD RATLIFF AND CONRAD G. MUELLER: **Synthesis of "on-off" and "off" responses in a visual-neural system**

FLOYD RATLIFF, B. W. KNIGHT, JUN-ICHI TOYODA, AND H. K. HARTLINE: **Enhancement of flicker by lateral inhibition**

FLOYD RATLIFF, B. W. KNIGHT, AND NORIL[illegible] GRAHAM: **On tuning and amplification by lateral inhibition**

FLOYD RATLIFF, B. W. KNIGHT, AND NORMAN MILKMAN: **Superposition of excitatory and inhibitory influences in the retina of *Limulus*: effect of delayed inhibition**

B. W. KNIGHT, JUN-ICHI TOYODA, AND FREDERICK A. DODGE, JR.: **A quantitative description of the dynamics of excitation and inhibition in the eye of *Limulus***

ROBERT SHAPLEY: **Fluctuations of the impulse rate in *Limulus* eccentric cells**

ROBERT SHAPLEY: **Effects of lateral inhibition on fluctuations of the impulse rate**

B. W. KNIGHT: **Dynamics of encoding in a population of neurons**

B. W. KNIGHT: **The relationship between the firing rate of a single neuron and the level of activity in a population of neurons**

H. K. HARTLINE: **Visual receptors and retinal interaction**

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

GONOCOCCAL OPHTHALMIA NEONATORUM. Pierog, S., Nigam, S., Marasigan, D. C., and Dube, S. K. (Jewish Hosp. and Medical Ct., Brooklyn, New York). Am. J. Obstet. Gynecol. 122:589, 1975.

Gonococcal ophthalmia (proved by cultures) occurred in 11 infants delivered at the Jewish Hospital and Medical Center of Brooklyn (JHMCB) during a three and one-half-year period. Two more infants had conjunctivitis with presumptive evidence of gonococci (Gram stain of eye discharge). Silver nitrate was instilled in the eyes of the neonates by registered nurses. Maternal histories of these infants showed lack of prenatal care in ten, history of gonorrhea in pregnancy in three, and positive serology (STS) in two; ten of the mothers were unmarried. The over-all incidence of gonorrhea at the JHMCB prenatal clinic screening program is very low (0.02%). Prevention of neonatal gonorrheal ophthalmia depends on: vigorous screening of mothers at delivery as well as during prenatal visits, careful attention to instillation of silver nitrate in the neonates' eyes, development of serologic tests for gonorrhea, and improved bacteriologic methods for culturing the organism. (2 tables, 17 references)—Authors' abstract

ANNALES D'OCULISTIQUE

GENETICS AND CONGENITAL BLINDNESS. (French) François, J. (Univ. Ghent, Belgium). Ann. Ocul. 208:417, 1975.

Congenital blindness may be from acquired disease or may be hereditary. The author reviews the genetic, hereditary causes of congenital blindness. He points out that that it is important to establish the presence or absence of hereditary factor since if it is hereditary it is important to determine the type of inheritance. If the disease is autosomal recessive the risk for sibs is 25% but zero for descendants assuming that no further intermarriage takes place. If, on the other hand, the disease is autosomal dominant, the risk for sibs as well as for descendants is 50%. If the disease is recessive sex-linked, the risk exists only for boys of a mother who is a carrier and is 50%. (15 figures, 80 references)—David Shoch

ANNALS OF INTERNAL MEDICINE

CEREBRAL DISORDERS OF VISION IN SYSTEMIC LUPUS ERYTHEMATOSUS. Brandt, K. D., Lessell, S., and Cohen, A. S. (Dept. Med., Boston City Hosp., Boston, Mass.). Ann. Intern. Med. 83:163, 1975.

Sensory neuro-ophthalmic abnormalities due to cerebral lupus erythematosus, with involvement of visual pathways posterior to the optic chiasm, occurred in 12 patients with systemic lupus erythematosus. Five underwent detailed evaluation because of an hallucination, four for visual loss, and three for both. Hallucinations were either unformed (for example, bright lights, straight lines) or highly formed (for example, faces), in which case they were invariably recognized by the patient as inappropriate. In no instance did they occur in association with delirium, confusion, or use of hallucinogenic drugs. Patients with loss of vision had scotomas, homonymous field defects, and cortical blindness. These features indicate disease in the posterior cerebral artery circulation, a localization often supported by ancillary neurologic findings, for example, vocal cord paralysis, diminished gag reflex. Thus, various visual dysfunctions may occur in systemic lupus erythematosus due to cerebral vasculitis. At times they may be the most prominent and disabling feature of the disorder. (1 figure, 4 tables, 14 references)—Authors' abstract

SYSTEMIC AMYLOIDOSIS IN BEHCET'S DISEASE. Rosenthal, T., Bank, H., Aladjem, M., David, R., and Gafni J. (Heller Inst. Med. Res., Tel-Hashomer, Israel). Ann. Intern. Med. 83:220, 1975.

Behcet's original description of his disease consisted of the triad of aphthous stomatitis, genital ulceration, and iridocyclitis. These still

remain the major diagnostic criteria of the disease but there are many minor manifestations including cutaneous lesions, recurrent thrombophlebitis, thrombosis of the venae cavae, arteritis and arthritis. Three patients are reported here with many of the manifestations of Behcet's syndrome although only one had ocular involvement. However, all three had amyloidosis which was proved by histologic examination. The authors postulate that systemic amyloidosis is an intrinsic feature of Behcet's disease. (2 figures, 1 table, 26 reference)—David Shoch

Archives d'Ophtalmologie

HIGHLY HYDROPHILIC SOFT LENSES: OPTICAL INDICATIONS OF CONTINUOUS WEARING AND FITTING TECHNIQUE. (French) Lumbroso, P., Fourny, A., and Maussan, M. (Clermond-Ferrand, France). Arch. Ophtalmol. 35:341, 1975.

Thirty-three eyes have been fitted with permanent contact lenses and the authors feel that there are certain patients for whom these are ideal, e.g. those with severe rheumatism or other diseases of the hands and for very young children. The lenses are fitted in the hospital and the patients are observed over two days of constant wear. It is particularly important to see what the reaction is to wearing these lenses during the night. The measurements are made and the patient is discharged from the hospital. He is readmitted when his own lenses are ready and again watched twice daily for the first 48 hours to see if there are any ill effects from the constant wear. After this he is seen weekly and then monthly as an outpatient to follow the course of his wearing. Experience shows that it is sufficient to wash and sterilize these constantly-worn lenses every three to four months. The interval is different for different patients but in 33 eyes there have been no corneal ulcers.—David Shoch

Archives of Ophthalmology

RECESSION OF THE LATERAL RECTI; EFFECT OF PREOPRATIVE FUSION AND DISTANCE-NEAR RELATIONSHIP. Raab, E. L., and Parks, M. M. (Dept. Ophthalmol., Children's Hosp., Washington, D.C.). Arch. Ophthalmol. 93:584, 1975.

Overconvergence of up to 20 prism diopters in both constant and intermittent distance exodeviations gave a better chance for a satisfactory surgical result than did other initial postoperative positions of the eyes. A satisfactory surgical result was more likely to be maintained thereafter if fusion had been present just prior to lateral rectus surgery. Employing bilateral lateral rectus recession without regard to the preoperative distance-near relationship did not appear to influence the chance of obtaining a satisfactory alignment at five to eight weeks. Stability of the surgical results after recession of the lateral recti appeared to be lowest when preoperative convergence insufficiency was present. In exodeviation patients without convergence insufficiency, the relationship of distance to near alignments in ordinary use of the eyes did not influence the maintenance of a satisfactory binocular position after this procedure. (4 tables, 3 references)—Authors' abstract

British Journal of Ophthalmology

RETINAL VASCULAR OCCLUSIONS IN OPEN-HEART SURGERY. Williams, I. M. (Monash Univ., Dept. Med., Alfred Hosp., Victoria, Australia). Br. J. Ophthalmol. 59:81, 1975.

The present paper describes the pathological findings in the retina in two patients who died within a few hours after their second open-heart surgery. In the one patient the author observed during the operation the appearance of a white embolus occluding a branch of the inferonasal artery in the right eye and of highly refractile specks in the retina of both eyes. The embolus proved to consist of platelets enmeshed in fibrin and had probably originated from an injured vessel wall.

In the second case a white mass similar to a platelet embolus was found at the post-mortem examination. This mass proved to be mainly collagen, deep to the endothelial lining of the vessel which seemed to be patent. The author suggests this to be the endstage of an organized embolus of blood constituents which occurred during the earlier operation and became organized, with the endothelium reconstituted over it.

In trypsin digests of the retinas of both cases, capillary occlusions with two different materials were found: a fatty, osmophilic material and a more crystalline material which by electron probe x-ray microanalysis proved to have a high silicon content. The author relates the later finding to the use, in the earlier open-heart operation, of dimethylpolysiloxane with silica gel as a defoaming agent. Since there is no known physiological mechanism of excretion for this substance, it had to stay in the circulation where it gave rise to capillary occlusions. (5 figures, 17 references)—Peter C. Kronfeld

SURGICAL TREATMENT OF CHRONIC PAPILLEDEMA IN CHILDREN. Billson, F. A., and Hudson, R. L. (Royal Children's Hosp., Melbourne, Australia). Br. J. Ophthalmol. 59:92, 1975.

The authors' release cerebrospinal fluid into the orbital tissues by excising a triangular or elliptical piece of the optic nerve sheath on the nasal side of the nerve. In two children with intracranial hypertension, following otitis media and mastoiditis in one case and due to craniostenosis as part of Apert's syndrome in the other, the orbital operation was followed by subsidence of the papilledema, while the intracranial hypertension persisted. This optic nerve decompression should be reserved for cases in which visual function is endangered by papilledema due to intracranial hypertension which is not readily amenable to neurosurgical treatment. (6 figures, 14 references) —Peter C. Kronfeld

CYTOLOGY AS A GUIDE TO THE PRESENCE OF CHLAMYDIAL INCLUSIONS IN GIEMSA-STAINED CONJUNCTIVAL SMEARS IN SEVERE ENDEMIC TRACHOMA. Yoneda, C., Dawson, C. R., Daghfous, T., Hoshiwara, I., Jones, P., Messadi, M., and Schachter, J. (Univ. Calif., San Francisco, Calif.). Br. J. Ophthalmol. 59:116, 1975.

The materials for this study were conjunctival smears from school children living in a Tunisian desert community, in which trachoma is hyperendemic and seasonal bacterial conjunctivitis is highly prevalent. A total of 927 Giemsa-stained smears from individual eyes were examined for cell types and for chlamydial inclusions. In 93 out of this total such inclusions were identified. If the smear contained plasma cells, macrophages, blastoid and stem cells, in addition to polymorphonuclear neutrophils and separated epithelial cells, there was a 70% chance of the smear also containing inclusions.

The yield of chlamydial inclusions with the Giemsa technique and that of the fluorescent antibody method (FA) were compared in pairs of smears taken from 527 individual eyes in the same sitting. Giemsa detected trachomatous agent in 43 smears; the FA method concurred in 30 of these smears and yielded additional positive results in 24 Giemsa-negative smears. For laboratories with limited facilities, the Giemsa method, aided by cytology, is regarded as useful for the diagnosis of trachoma and inclusion conjunctivitis. (13 figures, 3 tables, 12 references)—Peter C. Kronfeld

MIOTICS IN CLOSED-ANGLE GLAUCOMA. Ganias, R., and Mapstone, R. (St. Paul's Eye Hosp., Liverpool, England). Br. J. Ophthalmol. 59:205, 1975.

In 20 cases of acute, closed-angle glaucoma, varying in duration from 15 hours to 21 days, the treatment was begun with 500 mg of acetazolamide intravenously, followed immediately by the first dose of 2% pilocarpine. One half of the patients received just two drops in 60 minutes while the other half of the patients was given about 10 instillations of more than one drop each. In a third group of ten patients (with acute angle-close glaucoma), the initial intravenous dose of acetazolamide was followed three hours later, by the same dose orally plus one drop of pilocarpine topically. All 30 patients were given one further drop of pilocarpine six hours after inception of treatment. The three forms of treatment were equally effective in the sense that in nine of the ten cases in each group the pressure dropped below 22 mm Hg within the first seven hours of treatment. The authors conclude that there is no logical reason for giving pilocarpine early, that is, when the pressure is high and the sphincter presumably unresponsive to miotics. Once the pressure has been lowered by acetazolamide, the sphincter may be expected to respond, and the ensuing miosis may bring about opening of the chamber angle. (1 table, 3 references)—Peter C. Kronfeld

British Medical Journal

ORBITAL BRUITS IN PATIENTS ON MAINTENANCE HEMODIALYSIS. Lancer, S. R., Guiterrez, L. F., and Pillay, V. K. G. (Abraham Lincoln School Med., Chicago, Ill.). Br. Med. J. 2:481, 1975.

Orbital bruits are frequently present in patients on hemodialysis. The bruits are probably due to anemia, but seem to be intensified by the arteriovenous fistula used for dialysis. (5 references)—Joel G. Sacks

Journal of Neurology, Neurosurgery and Psychiatry

HEMIANOPIC COLOR BLINDNESS. Albert, M. L., Reches, A., and Silverberg, R. (Dept. Neurol., Boston Univ. Medical Ctr. Boston, Mass.). J. Neurol. Neurosurg. Psychiatry 38:546, 1975.

A man developed cortical blindness after cerebral infarction in the distribution of both posterior cerebral arteries. When he recovered from this condition, he was found to be color blind in the left visual field, but not in the right. This unusual situation resulted in apparently contradictory performances on hemifield and free-field tasks of color discrimination, naming, and recognition. The contradictions may be explained by interhemispheric competition between a hemisphere which could discriminate colors and a hemisphere which was color blind. (1 table, 12 references)—Authors' abstract

Lancet

CHLORAMPHENICOL EYE-DROPS AND MARROW APLASIA. Carpenter, G. (Los Angeles, Calif.). Lancet 2:326, 1975.

A patient with completely aplastic bone marrow is reported who had no history of any drug intake. However, after a year of treatment of his aplastic anemia he recalled using eye-drops for some period in 1973. The eye-drops were found to contain chloramphenicol 5 mg per ml. Of the total of 10 ml in the bottle the patient used 6.5 ml for a maximum possible exposure of 32.5 mg of chloramphenicol. The author postulates that this may well have been the cause of his aplastic anemia. (1 reference)—David Shoch

New England Journal of Medicine

ADENOVIRUS 19, A CAUSE OF EPIDEMIC KERATOCONJUNCTIVITIS, NOT ACUTE HEMORRHAGIC CONJUNCTIVITIS. Dawson, C. R., O'Day, D., and Vastine, D. (Proctor Foundation, San Francisco, Calif.). N. Engl. J. Med. 293:45, 1975.

The keratoconjunctivitis caused by the newly discovered adenovirus 19 is a rather typical epidemic keratoconjunctivitis with many of the same characteristics as the usual "shipyard conjunctivitis" which is caused by adenovirus type 8. Although the original report of advenovirus 19 keratoconjunctivitis was called acute hemorrhagic conjunctivitis, the authors feel that this is a misnomer and that the term acute hemorrhagic conjunctivitis should be reserved for the short-lived conjunctivitis associated with enterovirus 70. (4 references)—David Shoch

PROGRESSIVE RUBELLA PANENCEPHALITIS LATE ONSET AFTER CONGENITAL RUBELLA. Townsend, J. J., Baringer, J. R., Wolinsky, J. S., Malamud, N., Mednick, J. P., Panitch, H. S., Scott, R. A. T., Oshiro, L. S., and Cremer, N. E. (Dept. Neurol., Univ. California, San Francisco, Calif.). N. Engl. J. Med. 292:990, 1975.

Three children are described with the characteristic findings of congenital rubella. Their conditions remained stable until a progressive neurologic disease developed in the second decade of life that was characterized by spasticity, ataxia, intellectual deterioration and seizures. High antibody titers to rubella virus in serum and spinal fluid were present in two. Extensive attempts to recover virus from brain and body fluids were unsuccessful. The brains of two patients became available and these showed a widespread progressive subacute panencephalitis mainly affecting white matter. It thus appears that the findings of congenital rubella are not static but actually involve all

systems and may in fact cause progressive deterioration later in life. (3 figures, 2 tables, 26 references)—David Shoch

Survey of Ophthalmology

MEDICAL TREATMENT OF TRAUMATIC HYPHEMA. Pilger, I. S. (Harbor Gen. Hosp., Torrance, Calif.). Surv. Ophth. 20:28, 1975.

Small hyphemas, that is, those occupying less than half the anterior chamber have an excellent prognosis and it probably makes very little difference whether or not the patient is hospitalized and placed at bedrest with binocular patches. The prognosis is generally good. However, hyphemas that occupy more than half the chamber need more rigorous treatment. These patients are best placed at bedrest and watched carefully. Increased intraocular pressure should be treated with appropriate drugs and if the pressure is not adequately lowered within 24 to 48 hours, surgical intervention is required. If the intraocular pressure is normal then surgical intervention is required only if there is a persistent, significant organized clot. (1 figure, 4 tables, 33 references)—David Shoch

Transactions of the American Academy of Ophthalmology and Otolaryngology

THE CASE FOR GENERAL ANESTHESIA. Lynch, S. (Manhattan Eye, Ear & Throat Hosp., New York, N.Y.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:559, 1975.

A group of 2,217 cataract operations performed with local anesthesia. The incidence of systemic disease was about the same and it was noted that about 85% of patients undergoing cataract surgery have a significant physical malady. In comparing the two series there was about the same incidence of all complications with the exception of iris prolapse which was more common in the series conducted with local anesthesia. There was one death in the entire group of patients studied and this was four days after a general anesthetic due to a myocardial infarction. The incidence is therefore about the same as that in a random non-hospitalized population. (2 tables)—David Shoch

ANESTHESIA FOR STRABISMUS SURGERY. Smith, R. B. (Dept. Anesthesiology, Eye and Ear Hosp., Pittsburgh, Pa.). Trans. Am. Acad. Ophthal. Otolaryngol. 79:568, 1975.

In this review of many large series of cases from the literature one reads that the crude mortality rate for ophthalmic surgery varies between 1 and 2 per 1,000. There are differences from series to series but these are not statistically significant nor is the difference between local and general anesthesia statistically significant. It is pointed out that the major portion of ophthalmic surgery done is either in the very young—strabismus or the very old—cataracts. (5 tables, 11 references)—David Shoch

PENETRATING KERATOPLASTY FOR HERPETIC KERATITIS—PROGNOSTIC AND THERAPEUTIC DETERMINANTS. Langston, R. H. S., Pavan-Langston, D., and Dohlman, C. H. (Cleveland Clinic, Cleveland, Ohio). Trans. Am. Acad. Ophthal. Otolaryngol. 79:577, 1975.

A review of grafting for herpetic keratitis shows a steady improvement over the years. The disease activity, regrafting and host vascularization are poor prognostic factors. The best results are obtained in patients treated with larger grafts, with the use of a running 10-0 nylon suture and with routine use of high levels of topically applied corticosteroids in the immediate post-operative period. (2 figures, 4 tables, 7 references)—David Shoch

PTERYGIUM MANAGEMENT BASED UPON A THEORY OF PATHOGENESIS. Paton, D. (Dept. Ophthalmol., Baylor Coll. Med., Houston, Tex.). Trans. Am. Acad. Ophthal. Otolaryngol. 79:603, 1975.

It is proposed that pterygia are a protective tissue mechanism resulting from actinic keratoconjunctivitis. They result as a response to chronic superficial corneal disease characterized by dry spots and dellen. Primary pterygia are best treated by simply avulsion or superficial excision of the pterygium head, preserving a smooth corneal contour. A recurrent pterygia associated with thinning of the cornea is best treated by a lamellar keratoplasty. (9 figures, 18 references)—David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings and lecturers must be received at least three months prior to the date of occurrence.

WILLS EYE HOSPITAL: ANNUAL CONFERENCE

The Wills Eye Hospital will present its Annual Conference at the Bellevue Stratford Hotel, Philadelphia, Jan. 29-31, 1976. Symposia and workshops will include sessions on vitreous and retinal diseases, oculoplastics, glaucoma, and related subjects. David Shoch will give the Bedell Lecture. For further information, write Gerard Shannon, M.D., Chairman, Annual Clinical Conference Committee, Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130.

NASSAU SURGICAL SOCIETY: 13TH ANNUAL CLINIC DAY

The Division of Ophthalmology of the Nassau Surgical Society will hold a one-day meeting Dec. 10, 1975, at the Nassau County Medical Center, East Meadow, Long Island, New York. For further information, write Elsa K. Rahn, M.D., Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554.

WASHINGTON HOSPITAL CENTER: SYMPOSIUM ON CLINICOPATHOLOGICAL CORRELATIONS OF OPHTHALMIC DISEASE

The Department of Ophthalmology of the Washington Hospital Center, Washington, D.C., will sponsor a symposium, "Correlations of Ophthalmic Disease," to honor Lorenz E. Zimmerman. It will be held at the Shoreham Hotel, Washington, D.C., March 26 and 27, 1976. For further information, write Harold I. Rodman, M.D., 1003 Spring St., Silver Spring, MD 20910.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY: ANNUAL PRESIDENT'S MEETING

The Puget Sound Academy of Ophthalmology will hold its annual President's Meeting Jan. 23 and 24, 1976, at the Washington Plaza Hotel, Seattle, Washington. The program will be a coordination of the two clinical areas, "Corneal Disease" and "Contact Lens Practice." Preceding the meeting, on Jan. 22, will be the annual Resident's Open Lecture. The program has been approved for A.M.A. Continuing Education Credit. For further information, write Charles Boylan, M.D., Secretary, 1601 16th Ave., Seattle, WA 98122.

BASCOM PALMER EYE INSTITUTE: SYMPOSIUM ON OPHTHALMIC PLASTIC AND CORNEAL SURGERY

The Bascom Palmer Eye Institute Department of Ophthalmology of the University of Miami School of Medicine and the Florida Lions Eye Bank at Miami will sponsor a symposium, "Ophthalmic Plastic and Corneal Surgery," April 11-16, 1976, at the Doral Beach Hotel, Miami Beach, Florida. Tuition for the course is $250; $125 for residents on application from their department heads. Checks should be made payable to Bascom Palmer Eye Institute. For further information, write Ophthalmic Plastic Surgery Symposium, Bascom Palmer Eye Institute, P.O. Box 520875, Biscayne Annex Miami, FL 33152.

BASCOM PALMER EYE INSTITUTE SYMPOSIA

The Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, will hold symposia in conjunction with the scientific dedication of its new eye care facilities, Bascom Palmer Eye Institute Anne Bates Leach Eye Hospital. Open House will be Jan. 10 and 11, 1976.

A neuro-ophthalmology symposium, "Diseases of the optic nerve," "Chiasm disturbances of ocular motility," and "Neuro-physiology of vision," will be held Jan. 6-9, 1976. The fee for the course is $300; $150 for residents.

A strabismus symposium will be held Jan. 9 and 10, 1976. The fee is $150; $75 for residents. A combined rate for both of the above mentioned courses is $400 for practitioners; $200 for residents on application from their department heads.

A vitreous-retinal-choroidal symposium, "Present concepts in diagnosis and treatment of malignant melanoma of the choroid," "Macular diseases—Diagnosis and treatment," and "Role of vitreous surgery in perforating injuries," will be held Jan. 12-15, 1976. The fee for the course is $325; $150 for residents.

For further information, write Bascom Palmer Eye Institute, P.O. Box 520875, Biscayne Annex, Miami, FL 33152.

Park Ridge Hospital: Intraocular Lens Seminar

The Department of Ophthalmology of Park Ridge Hospital, Rochester, New York, will hold a seminar on intraocular lenses Dec. 4, 1975. For further information, write G. Keefe Jackson, M.D., Program Chairman, Department of Ophthalmology, Park Ridge Hospital, P.O. Box 2800, Rochester, NY 14626.

Page and William Black Post-Graduate School of Medicine: Ophthalmic Plastic Surgery Course

The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine, New York, will offer a course entitled "Ophthalmic Plastic Surgery," Jan. 15 and 16, 1976, from 9 A.M. to 5 P.M. at the Mount Sinai Medical Center, New York City. Subjects to be covered include blepharoptosis, entropion, ectropion, enucleation, cosmetic blepharoplasty, blow-out fracture, eyelid reconstruction, lacrimal surgery, and the handling of acute trauma. The fee for the course is $250. For further information, write Registrar, Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, NY 10029; telephone (212)650-6737.

Doctor-to-Doctor Medical Journal Program

Doctors in the United States are asked to send their medical journals—after having read them—to colleagues overseas (Asia, Latin America, and Africa) who wish to have access to current medical literature but, because of either currency regulations or actual costs involved, cannot themselves subscribe to medical periodicals. Participants will be supplied with the name, address, and medical specialty of doctors in these areas who wish to receive much-wanted journals (particularly specialty journals) and will mail them directly to their overseas colleague. The "Doctor-to-Doctor" program is sponsored by the American Medical Association with the collaboration of the World Medical Association. Persons wishing to participate in the program should send their names, addresses, and titles of journals they would be willing to contribute to Doctor-to-Doctor Program, c/o The World Medical Association, Inc., 10 Columbus Circle, New York, NY 10019.

Personal

Frederick C. Blodi

Professor Frederick C. Blodi, long-time member of the Editorial Board of The American Journal of Ophthalmology, has been named chief editor of the Archives of Ophthalmology. Professor Blodi will succeed Henry F. Allen whose term expires in 1976.

Albert C. Esposito

Albert C. Esposito, of Huntington, West Virginia, was inaugurated president of the American Association of Ophthalmology at its annual meeting in Dallas, Texas, Sept. 19, 1975. Dr. Esposito received his M.D. degree "cum laudum" from Loyola University School of Medicine, is a recipient of the Stritch Medal Award, and currently is a member of the West Virginia legislature.

FIVE-YEAR OPHTHALMIC MEETING CALENDAR

For listings, write Bruce E. Spivey, M.D., Professor and Chairman, Pacific Medical Center, Department of Ophthalmology, P.O. Box 7999, San Francisco, CA 94120.

1975

NOVEMBER	29-DEC. 4	American Medical Association, Clinical Convention	Honolulu

1976

JANUARY	4-6	VI Afro-Asian Congress of Ophthalmology	Madras, India
	6-15	Dedication, new facilities, Bascom Palmer Eye Institute	Miami
	17	American Board of Ophthalmology (written)	Multiple sites
		Ophthalmic Knowledge Assessment Program, AAOO (written)	Multiple sites
MARCH	24-26	The Czechoslovak Ophthalmological Society	Prague, Czechoslovakia
APRIL	5-9	European Congress of Ophthalmology	Hamburg, Germany
	28-MAY 1	II World Congress on the Cornea	Washington, D.C.
MAY	7-10	American Board of Ophthalmology (oral)	Philadelphia
	14-16	American Ophthalmological Society	Kilauea, Hawaii
	16-21	Pacific Coast Oto-Ophthalmological Society	Seattle
JUNE	13-19	Club Jules Gonin Meeting	Lausanne, Switzerland
	26-JULY 1	American Medical Association, Annual Convention	Dallas
AUGUST	8-13	Asia Pacific Academy of Ophthalmology	Denpasar, Bali, Indonesia
OCTOBER	6-10	American Academy of Ophthalmology and Otolaryngology	Las Vegas
	11-15	American College of Surgeons, Clinical Congress	Chicago
	21-24	American Board of Ophthalmology	San Francisco
NOVEMBER	11-15	Association of American Medical Colleges	San Francisco
DECEMBER	2-5	American Board of Ophthalmology (oral)	Chicago
	4-8	American Medical Association Clinical Convention	Philadelphia

1977

MARCH	20-25	XI Pan American Congress of Ophthalmology	Santiago, Chile
APRIL	24-28	Pacific Coast Oto-Ophthalmological Society	Tucson, Arizona
	26-30	Association for Research in Vision and Ophthalmology	Sarasota, Florida
MAY	4-7	American Board of Ophthalmology (oral)	San Francisco
	15-20	Instituto Barraquer VII International Course	Barcelona
	30-JUNE 1	American Ophthalmological Society	Hot Springs, Virginia
JUNE	18-23	American Medical Association Annual Convention	San Francisco
SEPTEMBER	10-11	International Intra-ocular Implant Society	Coronado, California
OCTOBER	16-19	American Board of Ophthalmology (oral)	Philadelphia
	17-21	American College of Surgeons Clinical Congress	Dallas
NOVEMBER	6-10	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
DECEMBER	4-7	American Medical Association, Interim Convention	Chicago

1978

MAY	14-21	International Congress of Ophthalmology—Concilium Ophthalmologicum Universale	Kyoto, Japan
	29-31	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	16-20	American College of Surgeons Clinical Congress	San Francisco
NOVEMBER	5-9 (tentative)	Association of American Medical Colleges	New Orleans

1979

MAY	28-30	American Ophthalmological Society	Washington, D.C.
OCTOBER	22-26	American College of Surgeons Clinical Congress	Hot Springs, Virginia
NOVEMBER	4-8	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Chicago

TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETIES OF THE UNITED KINGDOM

Transactions of the Ophthalmological Societies of the United Kingdom, published since 1880 in a single volume, is now published in **four separate parts** as follows:

I. The Annual Congress of the O.S.U.K. (held in April, published in the Autumn)

II. The Oxford Congress (held in July, published in the Winter)

III. The Cambridge Symposium on *'The Eye in Connective Tissue Disease'* (held in September, published in the following Spring)

IV. Papers from the Irish, Scottish and provincial societies, Reports from affiliated organizations throughout the world, and the Annual Index (published in the Summer)

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February 27th—Cataract Surgery
Chairman, Richard C. Troutman, M.D.
Corneal Surgery
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Massachusetts Eye and Ear Infirmary

Anthony B. Nesburn, M.D.
Estelle Doheny Eye Foundation

For further information, contact:
George M. Haik, M.D.
1542 Tulane Avenue
New Orleans, LA 70112

AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY

The 1976 annual meeting and scientific assembly of the American Society of Contemporary Ophthalmology will be held February 29 through March 5 at the Americana Hotel, Bal Harbour (Miami Beach), Florida.

Under the direction of Dr. Jules Francois, Chairman; Dr. Herbert Kaufman, President; and Dr. Claes Dohlman, President-Elect, more than 50 leading ophthalmologists will hold seminars presenting the latest information in clinical ophthalmology and workshops in New Techniques of Cataract Surgery and Lens Implants, Microsurgery of the Eye, Oculoplastic Surgery, Cornea, Glaucoma, Retina, Strabismus, Pediatric Ophthalmology, Contact Lenses, Refraction, Gonioscopy, Stereoscopic Studies of the Anterior Segment—and other subjects.

Registrants will earn up to 40 CME credit hours acceptable in Category 1 for the AMA Physician's Recognition Award and for the ASCO Certificate of Advanced Studies in Ophthalmology.

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Faculty
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Miles A. Galin, M.D., New York—"Intra-Ocular Lenses"
Jared M. Emery, M.D., Houston—"Phaco-Emulsification"
Norman Sanders, M.D., Miami—"Keratoplasty"

Registration Fee $125

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ARGON LASER PHOTOCOAGULATION • SYMPOSIUM ON THE MACULA • SURGERY OF THE ORBIT
LACRIMAL SAC SURGERY • CORNEAL CONTACT LENSES • PLASTIC EYE SURGERY • OCULAR GENETICS
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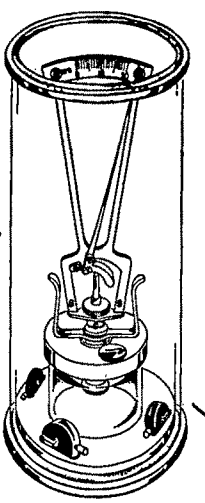
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Announcement of the

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PLACE:	Fairmont-Roosevelt Hotel, New Orleans
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FACULTY:	JAMES V. AQUAVELLA, M.D., Rochester, New York JOS. A. BALDONE, M.D., New Orleans PERRY S. BINDER, M.D., San Diego, California OLIVER H. DABEZIES, JR., M.D., New Orleans JACK HARTSTEIN, M.D., St. Louis, Missouri FRANK B. HOEFLE, M.D., New York City PAUL R. HONAN, M.D., Lebanon, Indiana HAROLD P. KOLLER, M.D., Cherry Hill, New Jersey WHITNEY G. SAMPSON, M.D., Houston, Texas
SPECIAL GUEST LECTURER:	HERBERT E. KAUFMAN, M.D., Gainesville, Florida Saturday, March 6, 1976—Corneal Surgical Techniques at Cataract Surgery to Facilitate Contact Lens Fitting
TOPICS:	Conventional hard contact lenses, hydrophilic soft gel lenses, silicone lenses, oxygen permeable hard contact lenses, aspheric, variable focus lenses, and intraocular lens implants.
PRE-MEETING COURSES: Wed., Mar. 3rd p.m.	Basic Lectures—by Industry—No additional fee.
LADIES DAY:	Activities Planned (Usually French Quarter & Garden District Tours) COME EARLY FOR THE MARDI GRAS SEASON, Feb. 28, March 1-2, 1976 Mardi Gras Day is Tuesday, March 2, 1976 Special convention hotel rates for Mardi Gras (to a limited number of registrants) Or you may avoid Mardi Gras by arriving New Orleans Wed. March 3rd
POST-COURSE	Gulf of Mexico Cruise out of the Port of New Orleans Call or write: George Scherer—Rownd Scherer Travel Service P.O. Box 368 Hammond, La. 70401 Ph: 504-345-4048
For further information contact:	Jos. A. Baldone, M.D. Roof, Delta Towers—Canal at Claiborne New Orleans 70112 USA Ph: 504-524-9729

1976 COURSE IS DEDICATED TO THE MEMORY OF THE LATE WM. BURTON CLARK, M.D.

The Bascom Palmer Eye Institute, Department of Ophthalmology of the University of Miami School of Medicine and the Florida Lions Eye Bank at Miami

Announces a Symposium on

OPHTHALMIC PLASTIC AND CORNEAL SURGERY

To be held at the Doral Beach Hotel
Miami Beach, Florida
April 11-16, 1976

Faculty for the course will include:

Dr. Jorge Buxton
Dr. Henry Clayman
Dr. Robert Dryden
Dr. Richard K. Forster
Dr. Arthur Grove, Jr.
Dr. Norman Jaffe
Dr. Richard Keates
Dr. Peter Laibson
Dr. James Major
Dr. Gordon Miller
Dr. Norman Sanders
Dr. Byron Smith
Dr. Richard Tenzel
Dr. Ira Weiner
Dr. John Wobig

This symposium will cover the corneal and ophthalmic plastic field. Multiple lectures will be given with ample time for panel discussion and questions from the registrants.

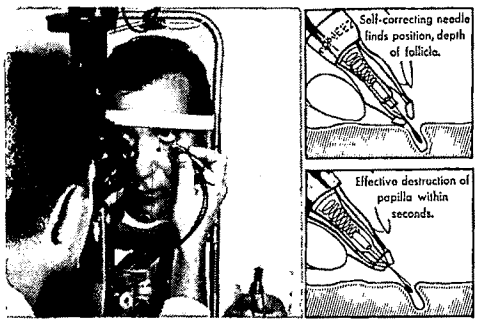
Afternoons will be set aside for recreation including tennis and golf tournaments. There will be planned entertainment for most evenings.

Tuition will be $250, breakfast included. Special rate of $125 available for residents upon application from their Department Head. Checks should be made payable to "Bascom Palmer Eye Institute" and mailed to Ophthalmic Plastic Surgery Symposium, Bascom Palmer Eye Institute, P.O. Box 520875, Biscayne Annex, Miami, Florida 33152.

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Would you like to have more tension-free office hours? You can by learning the PRACTICAL aspects of neuro-ophthalmology. This course is specifically directed toward the office practitioner—NOT the academician.

Here are some of the subjects we will be covering for you: examination methods, pupils, optic neuritis, headaches and diplopia.

Dates:	April 8 and 9, 1976
Place:	Houston, Texas Marriott Motor Hotel
Instructors:	J. Lawton Smith, M.D. Miami, Fla. J. A. McCrary III, M.D. Houston, Tx.
Fee:	$125.00 ($25.00 for residents)

For additional details write: Office Neuro-ophthalmology Course, J. A. McCrary III, M.D., Dept. of Ophthalmology, Baylor College of Medicine, Houston, Tx. 77025.

THE WASHINGTON HOSPITAL CENTER
DEPARTMENT OF OPHTHALMOLOGY

announces a symposium on

CLINICOPATHOLOGIC ASPECTS OF OCULAR DISEASE

Friday and Saturday, March 26, 27, 1976
Shoreham-Americana Hotel, Washington, D.C.

THE SYMPOSIUM WILL HONOR DR. LORENZ E. ZIMMERMAN

FACULTY:

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Ramon Font, M.D.
David Friendly, M.D.
William R. Green, M.D.
Marshall M. Parks, M.D.
L. Edward Perraut, M.D.
Harold I. Rodman, M.D.
Benjamin Rones, M.D.
Lorenz E. Zimmerman, M.D.

Panel discussions will feature PEDIATRIC OPHTHALMOLOGY, RETINAL DISEASES, and OCULAR and ADNEXAL TUMORS. In addition, there will be lecture presentations on other topics of clinicopathologic interest. The material presented will be clinically orientated with emphasis on diagnosis and therapy.

Registration fee: $175.00 Residents: $75.00

For information, contact:
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1003 Spring Street, Silver Spring, Maryland 20910

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February 20, 21, 1976

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Faculty

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Yale L. Fisher, M.D.
Edwin Trayner, M.D.
William Regan, M.D.
James Schutz, M.D.
Mr. Norman Pickering
Mr. William Farkas

For Information write: Yale L. Fisher, M.D., Ultrasound Clinic c/o Manhattan Eye, Ear & Throat Hospital, 210 East 64th Street, New York, New York 10021.

FELLOWSHIPS AVAILABLE

The Heed Ophthalmic Foundation provides fellowships for advanced study or research in ophthalmology. Applicants must be graduates of medical schools accredited by the American Medical Association and citizens of the United States. Deadline for submission of applications: November 30 for a fellowship starting the following July. Please direct all inquiries and requests for application forms to:

DAVID SHOCH, M.D.
Executive Secretary

THE HEED OPHTHALMIC FOUNDATION

303 EAST CHICAGO AVENUE
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February 12, 13, and 14, 1976

Mountain Shadows Resort

Scottsdale, Arizona

Sponsored by the Rockefeller and Abbie Prentice Eye Institute of St. Luke's Hospital Medical Center.

Faculty:

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Pittsburgh, Pennsylvania

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Indianapolis, Indiana

John Hetherington, Jr., M.D.
San Francisco, California

Gholam A. Peyman, M.D.
Chicago, Illinois

Richard C. Troutman, M.D.
Brooklyn, New York

Registration is $175. Participants will receive 18 elective hours credit.
For more information write:

Louis Rosenbaum, M.D., program chairman or
Jim Davis, director, Information Services
St. Luke's Hospital Medical Center
525 North 18th Street
Phoenix, Arizona 85006

WANTED: Ophthalmologist for position of Professor & Chairman, Dept. of Ophthalmology, State University of N.Y. at Buffalo (an Equal-Opportunity Employer). To administer the Dept. of Ophthalmology at the Medical School as well as the Affiliated Hospitals. Mature clinician, competent surgeon, accomplished academician, teacher & researcher, capable administrator. Contact: Dr. William J. Staubitz, Chairman, Search Committee, 716-831-8111.

CATARACT WORKSHOP

Phakoemulsification, Lens Implant, Vitrectomy and other modalities will be key subjects of a special workshop on **Cataract Surgery** at the 1976 AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY annual meeting (Feb. 29-Mar. 5, Americana Hotel, Bal Harbour/Miami Beach, Florida). The workshop will be presented in five afternoon sessions by Drs. Charles Kelman, Jack Hartstein, Norman Jaffe, Stanley Becker, Harvey Lincoff, Antonio Gasset and others.

The meeting will feature other workshops in Microsurgery and Stereoscopic Studies of the Anterior Segment; Contact Lenses in Aphakia and Corneal Diseases; Gonioscopy; Glaucoma; and Refraction.

More than 50 leading ophthalmologists will participate with the following chairmen: Cataract, David Paton; Retinal Diseases, Harvey Lincoff; Glaucoma, H. Saul Sugar; Cornea/External Diseases, Claes Dohlman; Pediatric Ophthalmology, Donelson Manley; Corneal Surgery, Herbert Kaufman; and Oculoplastic Surgery, Pierre Guibor. Jules Francois is Chairman of the entire meeting. Registrants earn 40 or more credit hours in CME.

Write: AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY
30 North Michigan Avenue, Chicago, Illinois 60602

THE CORNEA SERVICE AT WILLS EYE HOSPITAL WILL PRESENT A COURSE ON MANAGEMENT OF CORNEAL AND EXTERNAL DISEASES

DECEMBER 12-13, 1975

At the Marriott Hotel, City Line Avenue, Philadelphia, Pennsylvania

Guest Speakers:

James Aquavella, M.D.	Rochester, New York
Claes Dohlman, M.D.	Boston, Massachusetts
Dan Jones, M.D.	Houston, Texas
Jay Krachmer, M.D.	Iowa City, Iowa
George Waring, M.D.	Sacramento, California

and Cornea Staff, Wills Eye Hospital, Jefferson Medical College

Registration Fee: $150.00/include luncheons and banquet. Checks should be made payable to Corneal Conference and mailed to Cornea Service, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pa. 19130.

For registration and further information please write:
Peter R. Laibson, M.D., Director, Cornea Service
Wills Eye Hospital 215-L09-8200 ext. 273

Good for accreditation in category #1.

The Retina Service of Wills Eye Hospital

and

Jefferson Medical College of Thomas Jefferson University

announce a comprehensive course on

March 6 and 7, 1976

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Guest Lecturer—Paul Henkind, M.D., Ph.D.

Location: Jefferson Hall Commons, Philadelphia, Pa.

Tuition: $175.00. Special rate of $60.00 for residents and fellows.

Make checks payable to Retina Service, Wills Eye Hospital, and mail to Retina Service, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pa. 19130. Fee includes luncheons and Dinner.*

For programs, hotel reservations, wives' Bicentennial activities, write to:

Richard E. Goldberg, M.D.
Retina Service, Wills Eye Hospital
1601 Spring Garden Street
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*Wills Eye Ex-Retina Fellows Alumni Dinner—Friday night, March 5, 1976

THE AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY

and the

MOUNT SINAI SCHOOL OF MEDICINE (CUNY)
THE PAGE AND WILLIAM BLACK
POST-GRADUATE SCHOOL OF MEDICINE

Announce

THE SECOND ANNUAL PEDIATRIC OPHTHALMOLOGY SYMPOSIUM

May 19 to 23, 1976
Southampton Princess Hotel
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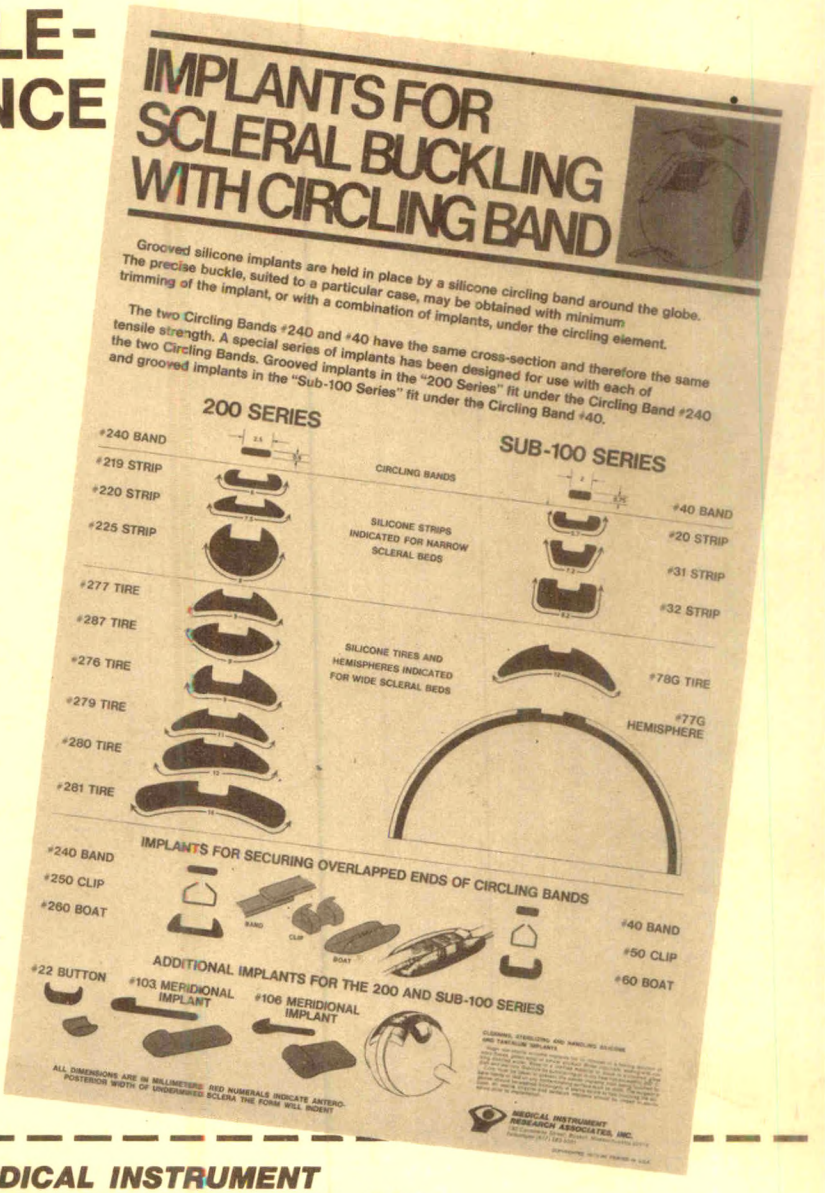
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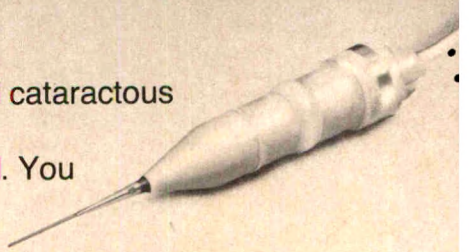
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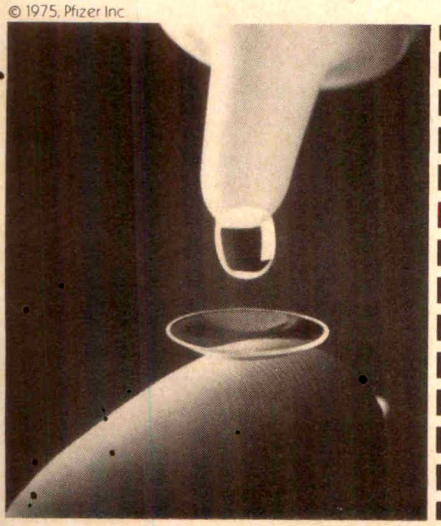
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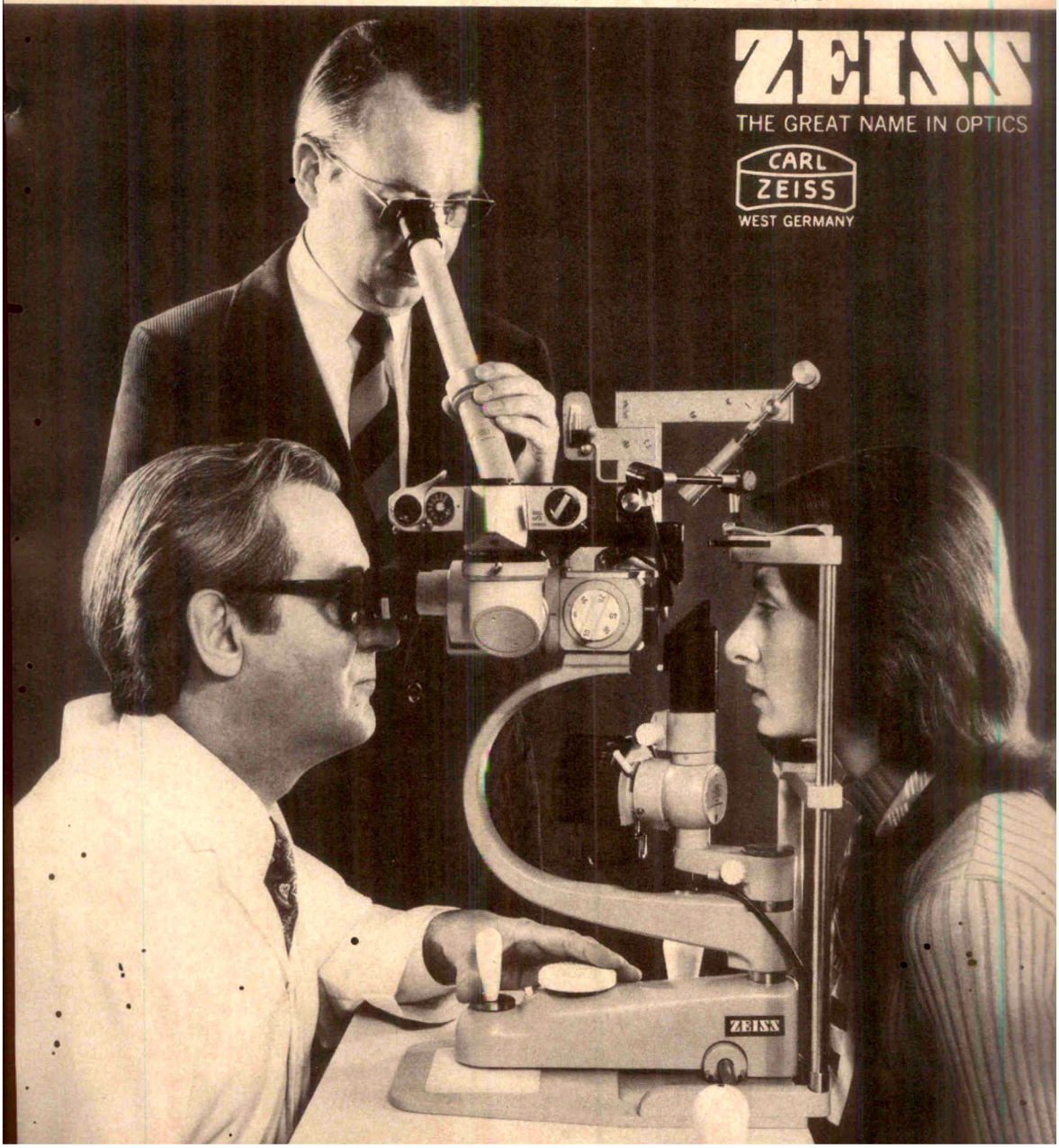
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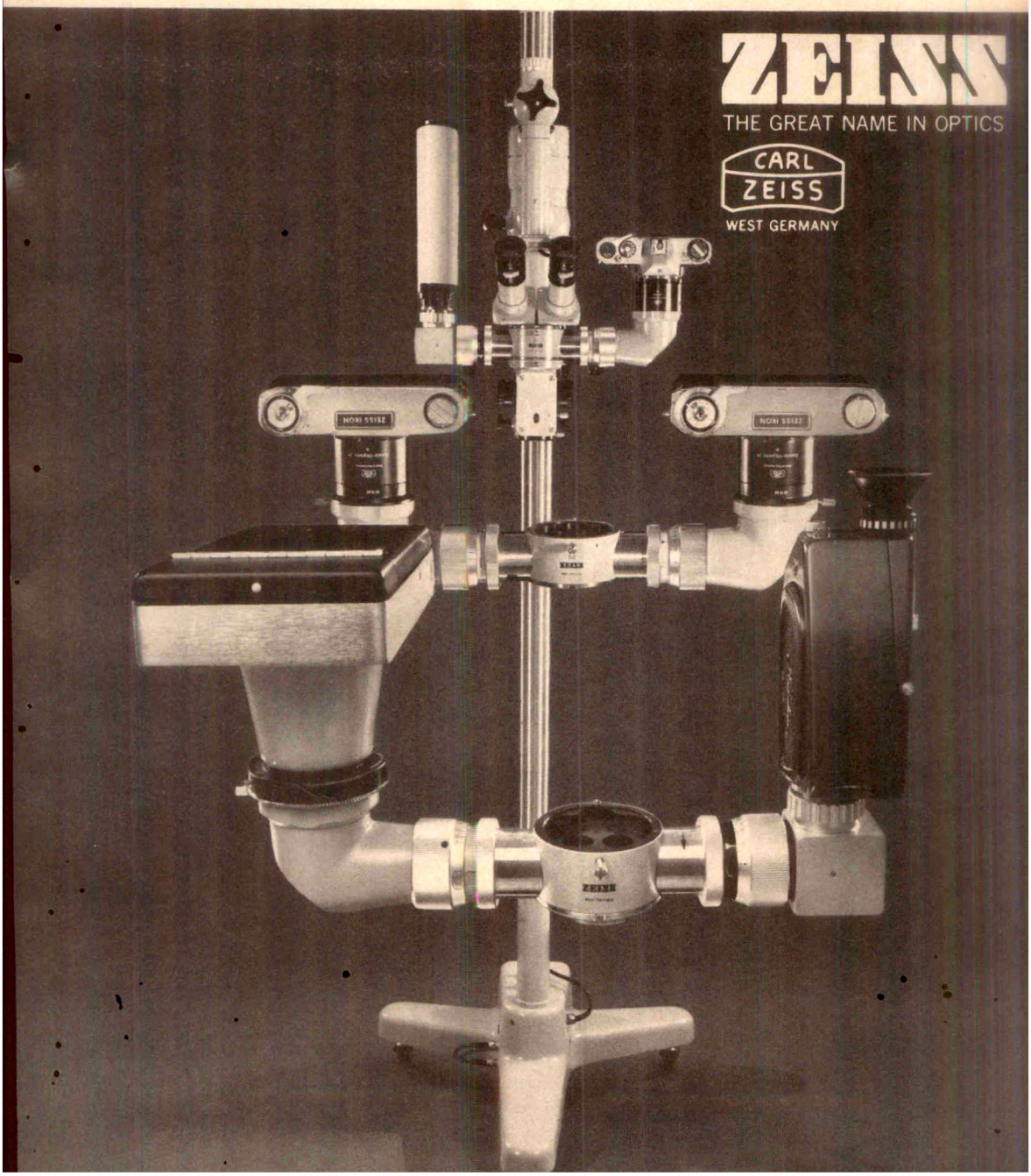
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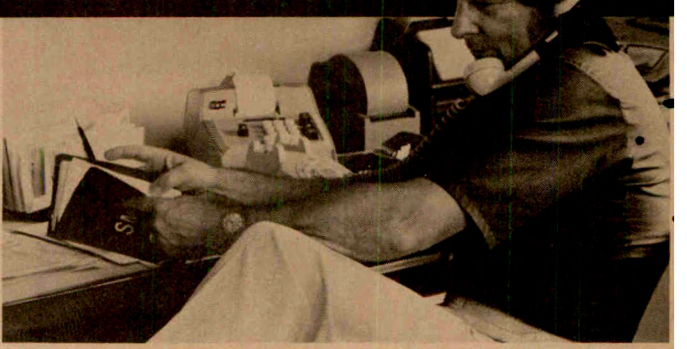
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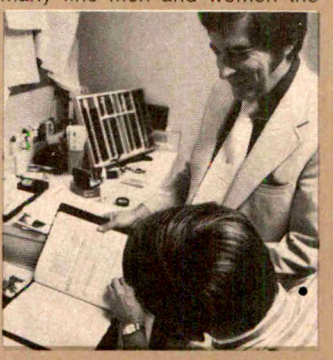
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"I try to review the current literature at least once every six weeks—even the Japanese and other foreign journals have English summaries—so I manage to stay up on things quite well. That way, I feel that I'm serving my doctors to the best of my ability. I may not have all the answers, but I'll usually have a pretty good idea where to find them."

Fred Ellis is just one of the many fine men and women the SMP Division of Cooper Laboratories has representing us. What Fred didn't say, was that he's a former histopathology and cardiographic laboratory technician and member of the American Society of Bacteriologists. Or that he is a graduate of Brooklyn College who majored in biology and chemistry, and studied advanced courses in physiology. "You never stop learning," Fred says, "or you become obsolete. That's the philosophy of the professionals I serve, and it's become my philosophy, too."

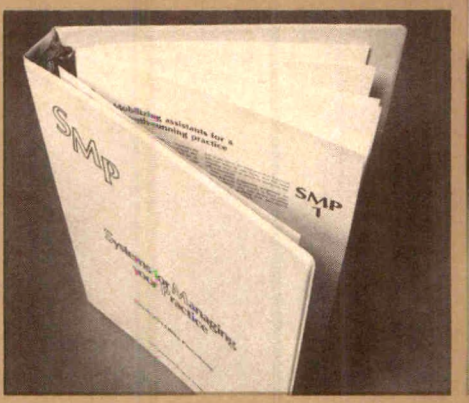


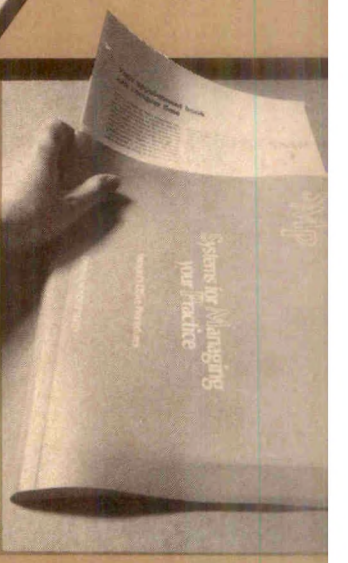
Maybe that's why Fred Ellis is currently enrolled as a candidate for Certification as a Medical Representative under a special pilot-program of required study at the Master's Degree level. Or why he studied business management courses for more than 7 years on a part-time basis. Business management courses might not seem to relate to the practice of Ophthalmology, "but even that background proved useful in Dallas," says Fred.

"Let me introduce you to the most comprehensive professional service program in the field of ophthalmology."

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Introduction of an exciting new—and completely free—service program developed for ophthalmologists by SMP together with the Medical Economics Company, and an opportunity to meet ophthalmology practice-management consultants Robert Hirsch and Marian Hetzger, resulted in over a thousand visitors to the SMP service area at the recent AAOO meetings in Dallas.

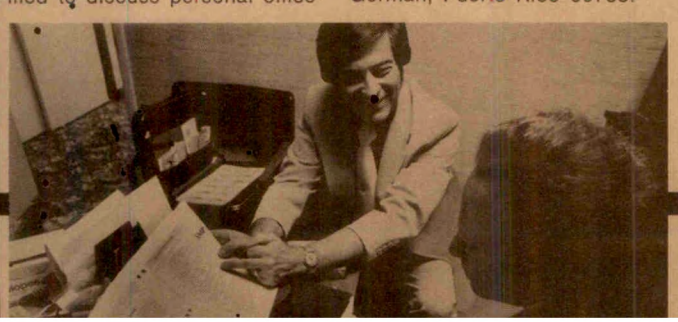
The new SMP **Systems for Managing your Practice** program is being inaugurated with a special audio-tape cassette series on "Collecting Professional Fees." It consists of two programs—one for you and one for your office assistant. In addition, it contains a printed outline to assist in the development of a personalized telephone collection solicitation tailored to your own specific requirements, and a checklist of important points to be covered during a conversation with a patient concerning a payment plan.

Another part of the *Systems* program includes regularly published pamphlets (and a binder to store them in for easy access) for both you and your office personnel—appropriate 'how-to' material to guide you in establishing efficient office practices.

As management consultants to more than 100 individual and group ophthalmology practices, Robert Hirsch and Marian Metzger were exceptionally well qualified to discuss personal office-management problems with AAOO attendees. As consultant editors to SMP's *Systems* program, they will continue to provide up-to-date views and guidance on important practice-management developments.

"SMP has an absolutely great idea to help you run your practice more efficiently."

To receive your complimentary copy of the first *Systems for Managing your Practice* audio-tape program: "Collecting Professional Fees" and to be listed to receive both the Physician and Assistant's monthly SMP Bulletins, contact your SMP representative, or write on your letterhead to *Systems for Managing your Practice,* SMP Division, Cooper Laboratories (P.R.), Inc. San German, Puerto Rico 00753.



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A REMINDER LISTING OF SMP OPHTHALMIC SPECIALTY PHARMACEUTICAL PRODUCTS

SMP

Service to Medicine Program: 1

RESIDENT'S CORNER:
"Coming out of a residency or relocating can be a puzzling and sometimes traumatic experience," says Fred Ellis, "but since we have SMP representatives throughout the country, many times we can help with information about an area that one of our doctors may be interested in."

"One of our SMP men had a line on a group practice opening in just 48 hours."

Part of SMP's new *Systems* program includes a series of articles on the pros and cons of various kinds of practice—for example, solo practice *vs.* group *vs.* P.A.—as well as data on regional geographical differences in ophthalmology practices. While this part of the *Systems* program is designed especially for Residents, any ophthalmologist who might be contemplating a career change can have copies while supplies last.



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Pilocar® Twin Pack
(pilocarpine hydrochloride)

Composition: PILOCAR Ophthalmic Solutions are buffered, stabilized solutions of pilocarpine hydrochloride and hydroxypropyl methylcellulose. The solutions are available in concentrations of 0.5%, 1%, 2%, 3%, 4% and 6% pilocarpine hydrochloride. All the concentrations, in addition to the respective amount of pilocarpine, contain:
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in an aqueous, buffered, stabilized solution containing potassium chloride, boric acid and sodium carbonate.

Action: As a miotic for treatment of glaucoma, especially open angle glaucoma.

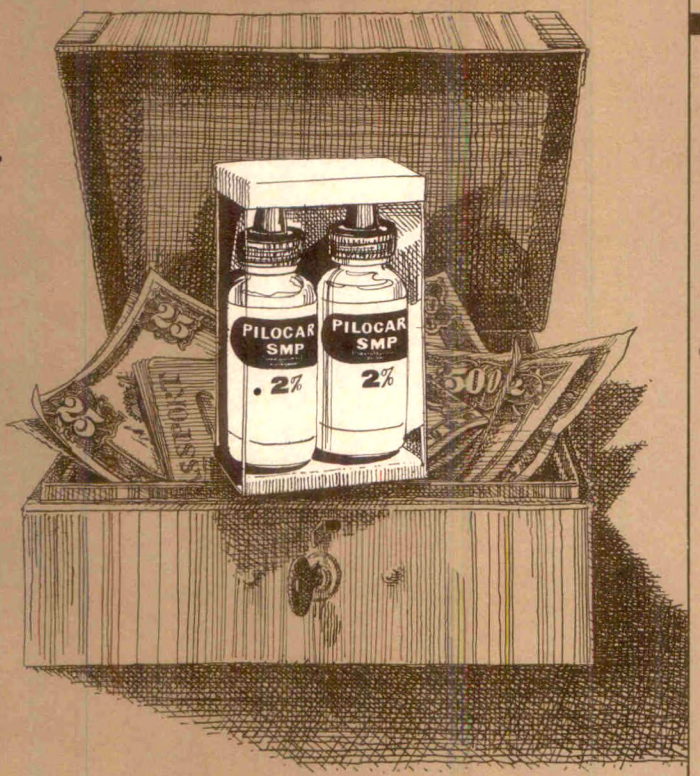
Indications: As a miotic in the treatment of glaucoma, more specifically, the chronic simple glaucoma of the open angle type. While the closed angle glaucoma differs completely from the open angle glaucoma, PILOCAR Ophthalmic may be used to relieve the tension in patients seen early, during hospital diagnostic tests, and prior to surgery. The most prevalent clinical application for PILOCAR is in the treatment of glaucoma simplex (open angle or chronic glaucoma). PILOCAR acts as a miotic to contract the pupil and reduce the intraocular pressure thereby attaining the desired relief. In acute glaucoma, the objective aims at opening the anterior chamber to lower intraocular pressure by medical means, i.e., PILOCAR, for at least 12 hours prior to emergency surgery.

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Please see brief summary on opposite page.

PILOCAR® TWIN PACK
(pilocarpine hydrochloride)

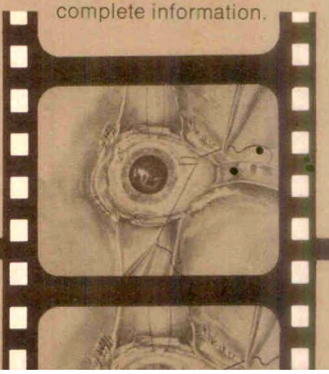
"A classic for the cost-conscious patient."



"I'd be willing to bet that nearly every ophthalmologist has seen at least one of SMP's films."

The SMP Memorial Film Library is one of the most comprehensive of its kind. "Some of the Ophthalmologists in the Miami area have a film version of the old Journal Clubs," reports Fred Ellis. "They look over the SMP film catalog and order films months in advance. Then they review and report on them, along with articles from the current journals."

You may find one of the SMP films useful for instructing a para-professional group on a specific surgical technique, or perhaps for use in a review of certain phases of ophthalmic practice with non-specialists. Don't hesitate to see your SMP representative or write to SMP Division, Cooper Laboratories for complete information.



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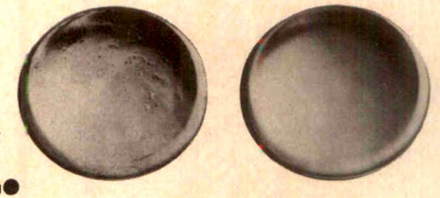
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ADVANCES IN UVEAL SURGERY, VITREOUS SURGERY, AND THE TREATMENT OF ENDOPHTHALMITIS

By **GHOLAM A. PEYMAN, M.D.**, Associate Professor of Ophthalmology &
DONALD R. SANDERS, M.D., Clinical Instructor in Ophthalmology;
both University of Illinois Eye and Ear Infirmary,
Abraham Lincoln School of Medicine, Chicago, Illinois

The authors' intent is to familiarize resident and practicing ophthalmologists with the past and present approaches to problems in three rapidly advancing areas of ophthalmology. UVEAL SURGERY—with emphasis on the differential diagnosis and surgical management of malignant uveal melanoma. Techniques of iridectomy, iridocyclectomy, and full-thickness eye wall resection are described as well as a technique for sclerochorioretinal biopsy for diagnosis of degenerative or inflammatory disease of the retina and choroid. All the surgical techniques are demonstrated with illustrations and operative views. VITREOUS SURGERY—discussed with the primary emphasis on the modern methods of vitreous surgery and the use of automated vitreous suction, cutting, and infusion instruments. Indications, pre-operative evaluation, surgical techniques, treatment and prevention of complications, and clinical results (including pre- and postoperative photos) of vitrectomy with the Peyman Vitrophage are described in detail. TREATMENT OF ENDOPHTHALMITIS—discusses the various antibiotics used clinically with respect to their spectrum and penetration after administration by systematic, topical, subconjunctival, and intravitreal routes. A step-by-step procedure is outlined for the diagnosis and treatment of a presumed endophthalmitis including the technique for intravitreal injection of antibiotics.

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The basic rationale behind the use of potent ophthalmic steroids such as FML and Pred Forte is to maintain functional integrity of the eye. In general, as long as evidence of active inflammation persists, it may be hazardous to discontinue steroid therapy. Use of potent steroids may in fact help preserve the ocular structure.[1]

When not to use potent steroids. Despite their usefulness, there are times when potent steroids (and mild ones too, for that matter) should be used with extreme caution – or not at all. It is generally agreed that untreated purulent infections, most viral diseases and ocular fungal infestations should be considered as contraindications to the use of these agents.

Indications and methods of use. Either FML or Pred Forte may be used to treat moderately severe to severe steroid responsive inflammatory conditions such as iritis, uveitis, iridocyclitis, episcleritis and resistant ocular allergy. In addition, data[2] made available recently attest to the usefulness of FML in long-term treatment of inflammation following cataract removal and keratoplasty. The patient photos to the right demonstrate the effectiveness of both FML and Pred Forte in severe ocular inflammation.

The usual method of administering either FML or Pred Forte is to instill one or two drops into the conjunctival sac two to four times a day. But to provide maximum therapeutic effectiveness when the severity of the inflammation dictates, the dosage can be *safely* increased to two drops every hour during the first 24 to 48 hours

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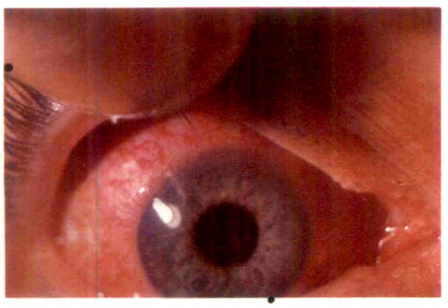
ACTIONS Inhibition of the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. Adrenocorticosteroids are capable of producing a rise in intraocular pressure. In clinical studies on patients' eyes treated with both dexamethasone and fluorometholone, fluorometholone demonstrated a lower propensity to increase intraocular pressure than did dexamethasone. **INDICATIONS** For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **CONTRAINDICATIONS** Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **WARNINGS** Steroid medication in the treatment of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by presence of steroid medication. Safety and effectiveness have not been demonstrated in children of the age group 2 years or below. Use In Pregnancy: Safety of the use of topical steroids during pregnancy has not been established. **PRECAUTIONS** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intraocular pressure should be checked frequently. **ADVERSE REACTIONS** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe. **DOSAGE AND ADMINISTRATION** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

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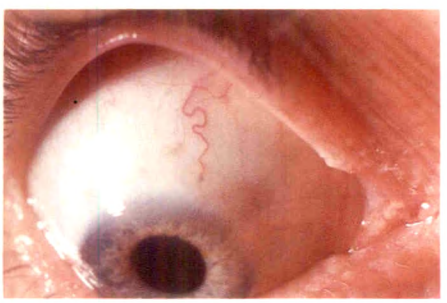
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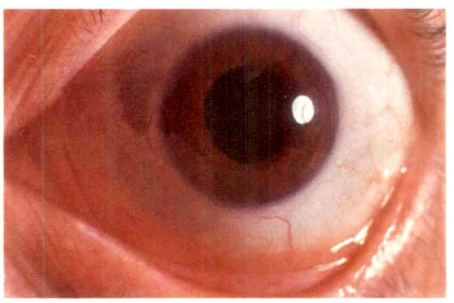
Patient CH. White male. Age 46. Acute episcleritis secondary to rheumatoid arthritis. Treatment started 2/24: FML one drop every hour for 48 hours then one drop every two hours for 36 hours then one drop every four hours thereafter.



Patient LV. White male. Age 57. Acute episcleritis. Treatment started 2/27: Pred Forte one drop every hour for 48 hours then one drop every two hours for 36 hours then one drop every four hours thereafter; warm compresses and scopolamine ointment twice daily.



Patient CH on 3/9. FML therapy stopped.



Patient LV on 3/12. Pred Forte therapy stopped.

References

1. Leopold, I.H. The steroid shield in ophthalmology. Trans Amer Acad Ophth & Oto 71:273–289, 1967.

2. Castroviejo, R. Data presented at 79th American Academy of Ophthalmology and Otolaryngology, Dallas, Oct. 1974.

3. Leibowitz, Howard M., Data presented at 79th American Academy of Ophthalmology and Otolaryngology, Dallas, Oct. 1974.

Photos by Dr. Ira Abrahamson, Cincinnati, Ohio

Pred Forte® (prednisolone acetate) 1% Sterile Ophthalmic Suspension

INDICATIONS For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **CONTRAINDICATIONS** Acute untreated purulent ocular infections, acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, ocular tuberculosis, and fungal diseases of the eye, and sensitivity to any components of the formulation. **WARNINGS** 1. In those diseases causing thinning of the cornea, perforation has been reported with the use of topical steroids. 2. Since PRED FORTE® contains no antimicrobial, if infection is present appropriate measures must be taken to counteract the organisms involved. 3. Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids. 4. Use of steroid medication in the presence of stromal herpes simplex requires caution and should be followed by frequent mandatory slit-lamp microscopy. 5. As fungal infections of the cornea have been reported coincidentally with long-term local steroid applications, fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use. 6. Use of topical corticosteroids may cause increased intraocular pressure in certain individuals. This may result in damage to the optic nerve with defects in the visual fields. It is advisable that the intraocular pressure be checked frequently. 7. Use in Pregnancy – Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. **PRECAUTIONS** Posterior subcapsular cataract formation has been reported after heavy or protracted use of topical ophthalmic corticosteroids. Patients with histories of herpes simplex keratitis should be treated with caution. **ADVERSE REACTIONS** Increased intraocular pressure, with optic nerve damage, defects in the visual fields. Also posterior subcapsular cataract formation, secondary ocular infections from fungi or viruses liberated from ocular tissues, and perforation of the globe when used in conditions where there is thinning of the cornea or sclera. Systemic side effects may occur with extensive use of steroids. **DOSAGE AND ADMINISTRATION** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

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British Journal of Ophthalmology

July 1975 Vol. 59 No. 7

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Atypical cotton-wool spots. *I. Egerer and H. Freyler*

Retinal macroaneurysms. *P. E. Cleary, E. M. Kohner, A. M. Hamilton, and A. C. Bird*

Treatment of malignant meningitis in retinoblastoma. *C. E. Stannard, R. Sealy, D. Sevel, and F. A. Brinton*

Therapeutic surgery in failures of medical treatment for fungal keratitis. *R. K. Forster and G. Rebell*

Dematiaceous fungal keratitis. Clinical isolates and management. *R. K. Forster, G. Rebell, and L. A. Wilson*

Corneal dellen in the limbal approach to rectus muscle surgery. *H. H. Tessler and M. J. Urist*

Genetic analysis of cover test measures and AC/A ratio in human populations with varying incidences of strabismus. *A. J. Mash, J. P. Hegmann, and B. E. Spivey*

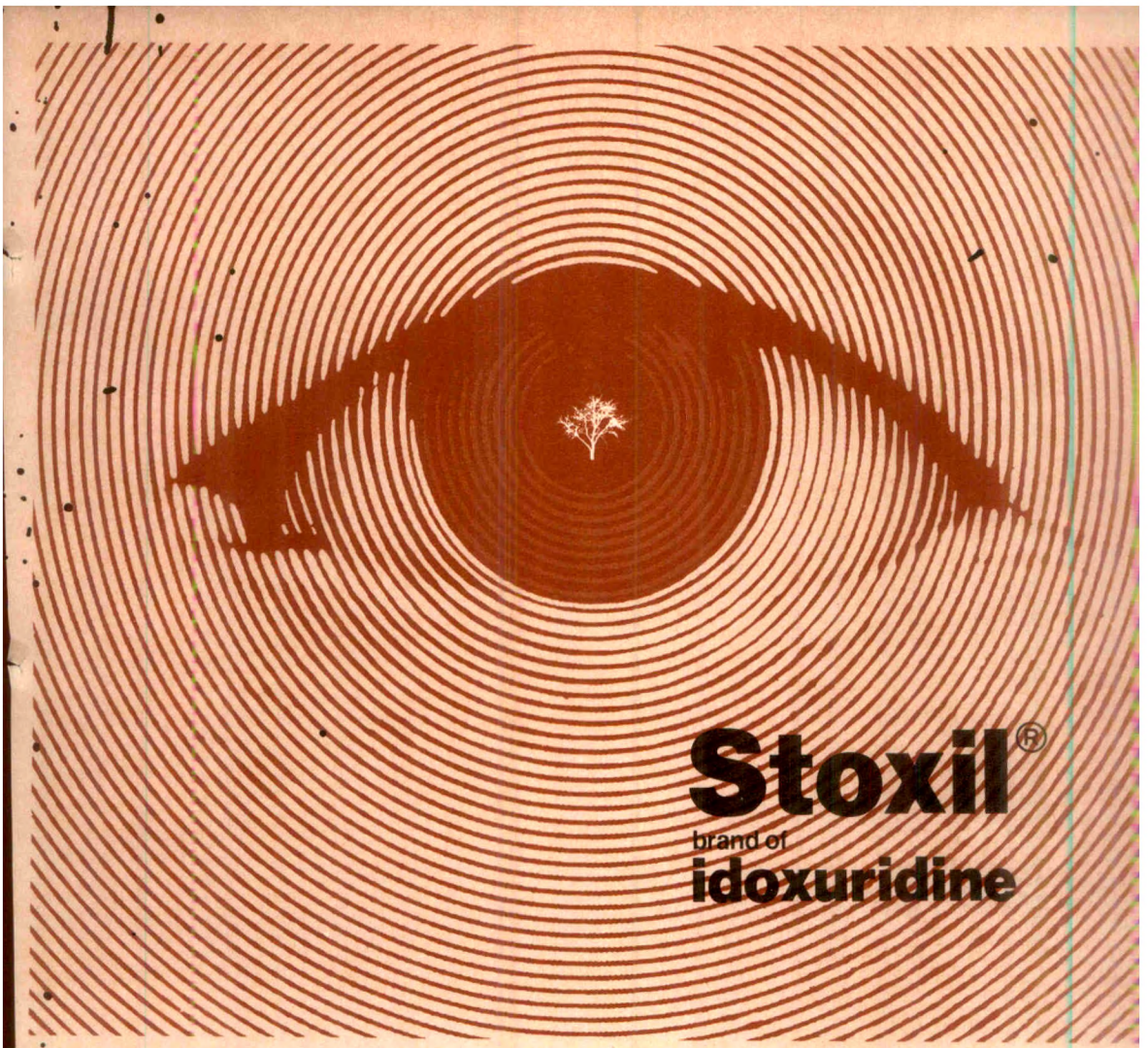
Superior oblique tendon sheath syndrome. *J. H. Sandford-Smith*

Ross' syndrome (tonic pupil plus). *T. R. Hedges and E. W. Gerner*

The biter bit. *W. O. G. Taylor*

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Stoxil®

brand of

idoxuridine

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Only in the treatment of herpes simplex keratitis.

Description: 'Stoxil' Ophthalmic Solution contains idoxuridine (5-iodo-2'-deoxyuridine) 0.1% (1 mg./ml.) in distilled water; sterile when packaged. Preserved with thimerosal, 1:50,000. 'Stoxil' Ophthalmic Ointment contains idoxuridine 0.5% (5 mg./gram) in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

Contraindications: Contraindicated in patients with known or suspected hypersensitivity to any of its components.

Warning: Usage in Pregnancy—Idoxuridine should be administered with caution in pregnancy or in women of childbearing potential. Although teratogenic effects were reported in one study with rabbits when idoxuridine was instilled into the eye, these effects were not observed in a subsequent, more detailed study, even at doses substantially higher than those in the preceding study.

Precautions: Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

'Stoxil' Ophthalmic Solution should not be mixed with other medications.

Adverse Reactions: Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally, corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

How Supplied: 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

Stability: The Solution should be stored in refrigerator until dispensed. 'Stoxil' Ophthalmic Ointment does not require refrigeration.

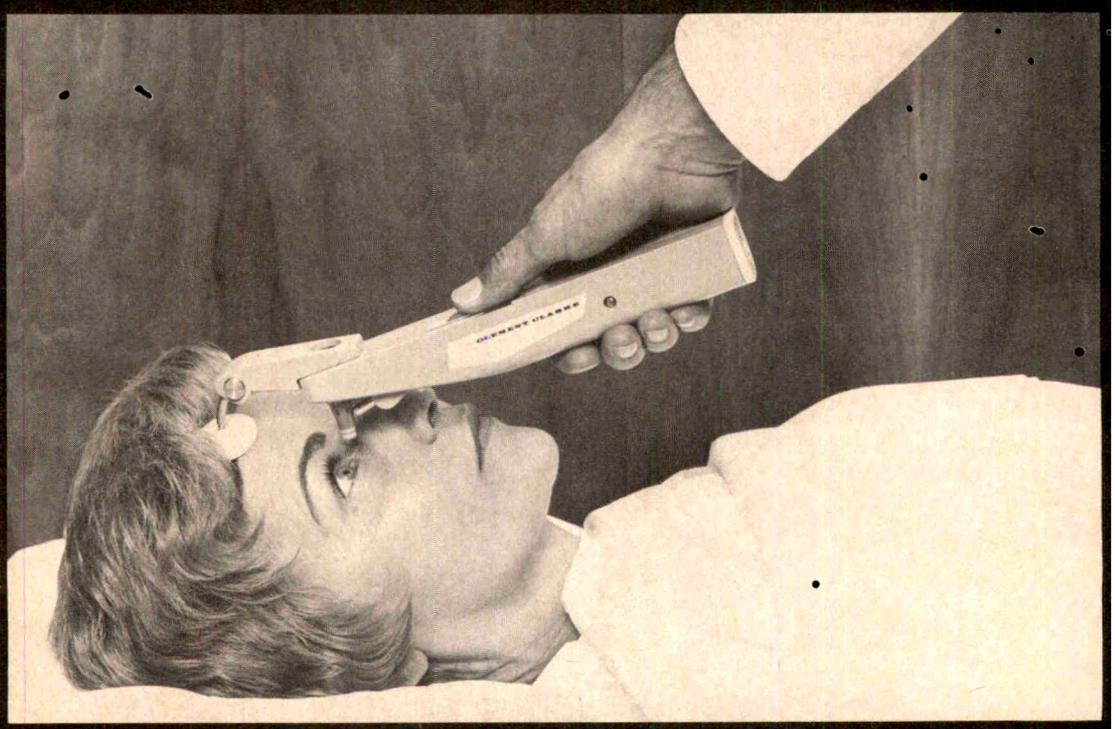
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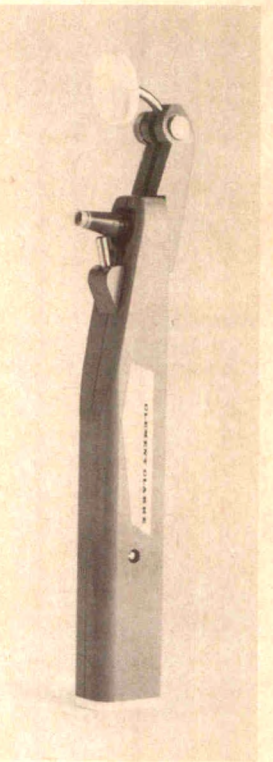
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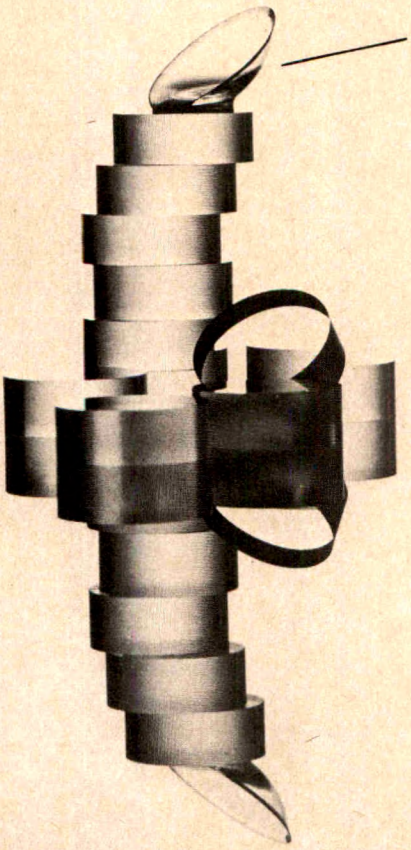
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(hefilcon A)

Contact Lens PHP*

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A division of Continuous Curve Contact Lenses, Inc.
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HydroCurve™ Soft Lenses, Inc. *PHP (U.S. Pat. 3,721,657) Trademark of Automated Optics, Inc.

HYDROCURVE™ (hefilcon A) CONTACT LENS

fabricated from PHP* polymer (poly (2-hydroxyethyl methacrylate) 46% Water 54%)

DESCRIPTION—The HydroCurve℠ (hefilcon A) Contact Lens PHP* is a hemispherical shell of approximately 14 mm. chord diameter and 0.1 to 1.0 mm. thickness. It consists of 46% poly (2-hydroxyethyl methacrylate) and 54% water by weight when immersed in normal saline.

ACTIONS—In its hydrated state a HydroCurve℠ (hefilcon A) Contact Lens PHP* becomes soft and pliable. When placed on the human cornea the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43.

INDICATIONS—HydroCurve℠ (hefilcon A) Contact Lenses PHP* are indicated for the correction of visual acuity in persons with nondiseased eyes who have spherical ametropias; refractive astigmatism of 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS—HydroCurve℠ (hefilcon A) Contact Lenses PHP* are contraindicated by the presence of any of the following conditions:

1. Acute and subacute inflammations of the anterior segment of the eye.
2. Any eye disease which affects the cornea or conjunctiva.
3. Insufficiency of lacrimal secretion.
4. Corneal hypoesthesia.
5. Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Medicants and Eye Drops: The HydroCurve℠ (hefilcon A) Contact Lens PHP* must be stored ONLY in BOILnSOAK℠ Solution. No ophthalmic solutions or medicants, including conventional contact lens solutions, can be used by HydroCurve℠ (hefilcon A) Contact Lens PHP* wearers prior to or while the lens is in place on the eye. Also, no solutions, including conventional contact lens solutions, other than BOILnSOAK℠ and the recommended cleaners BOILnSOAK℠ or Pliagel℠ or Soft/Mate℠ may be used on the HydroCurve℠ (hefilcon A) Contact Lens PHP* when the lens is off the eye.

Abrasions and Infections: If the lenses become less comfortable to the wearer than when they were first placed on the wearer's corneas, this may indicate the presence of a foreign body. The lens should be removed immediately and the patient examined. If any eye abrasion, ulceration, irritation or infection is present, a physician should be consulted immediately.

Lens Sanitation: Patients must adhere to recommended daily sanitary care of the HydroCurve℠ (hefilcon A) Contact Lenses PHP*. Failure to follow this procedure may result in development of serious ocular infections.

Wearing Restrictions: The HydroCurve℠ (hefilcon A) Contact Lens PHP* should be removed before sleeping or swimming or in the presence of noxious and irritating vapors.

Visual Blurring: When visual blurring occurs the lens must be removed until the condition subsides.

PRECAUTIONS

Storage: HydroCurve℠ (hefilcon A) Contact Lenses PHP* must be stored ONLY in BOILnSOAK℠ Solution. If left exposed to air, the lenses will dehydrate. If a lens dehydrates, it should be soaked in BOILnSOAK℠ Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: HydroCurve℠ (hefilcon A) Contact Lenses PHP* must be BOTH cleaned and disinfected daily. One procedure does not replace the other. CLEANING is necessary to remove mucus and film from the lens surface. This can be accomplished by using either BOILnSOAK℠ or Pliagel℠ or Soft/Mate℠ on a daily basis. Excessive deposits may damage the lens; therefore, if this occurs, review care of lens with patient.

DISINFECTING with the Hydrotherm℠ Patient Unit and BOILnSOAK℠ Solution has been shown to prevent the growth of certain organisms, namely Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Herpes simplex, on the lens and in the HydroCurve℠ Carrying Case with the porta-FLOW® Transfer Unit (basket).

HydroCurve℠ (hefilcon A) Contact Lenses PHP* must be cleaned daily with fresh BOILnSOAK℠ or Pliagel℠ or Soft/Mate.℠ Fresh BOILnSOAK℠ Solution must be used daily for storing the lenses. The HydroCurve℠ Carrying Case must be emptied and refilled with fresh BOILnSOAK℠ Solution just before disinfecting the lenses.

If a Hydrotherm℠ Patient Unit is not available for disinfecting the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.

Hygiene: Patients must be instructed to wash and rinse hands thoroughly, and dry with a lint-free towel before handling the lenses.

Cosmetics, lotions, soaps and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS—Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, patients may be instructed to apply a few drops of BOILnSOAK℠ Solution and wait until the lens moves freely before removing it.

Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms.

Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION—Conventional methods of fitting contact lenses do not apply to HydroCurve℠ (hefilcon A) Contact Lenses PHP*. For a detailed description of the fitting technique, refer to the HydroCurve℠ Fitting Guide, additional copies of which are available from: Soft Lenses, Inc., 8006 Engineer Road, San Diego, California 92111.

There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

Day	Maximum Wearing Time (Continuous Hours)	Day	Maximum Wearing Time (Continuous Hours)
1	3	8	8
2	3	9	8
3	4	10	10
4	4	11	12
5	6	12	14
6	6	13	15
7	8	14	all waking hours*

*Lenses should never be worn 24 hours a day.

Care must be taken on the initial visit to assure that the patient is supplied with a HydroCurve℠ Patient Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.



In Use Durability: With normal use and patient care, HydroCurve℠ (hefilcon A) Contact Lenses PHP* have been shown to be durable for a minimum of one year.

HOW SUPPLIED—Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the base curve, dioptric power, diameter, thickness and the manufacturing lot number of the lens.

To assure proper lens care and handling, each HydroCurve℠ patient must be supplied with a complete HydroCurve℠ Patient Care Kit.

The HydroCurve℠ Patient Care Kit is a package required for lens cleaning, disinfecting and storing consisting of the following:

porta-FLOW® Transfer Unit (basket)	Cat. # 1001
HydroCurve℠ Carrying Case	Cat. # 1002
Hydrotherm℠ Patient Unit	Cat. # 1003
BOILnSOAK℠ Solution	Cat. # 1004
Pliagel℠ Sterile Cleaner (optional) or	Cat. # 1005
Soft/Mate℠ Sterile Cleaner (optional)	Cat. # 1006
Patient Instructions	Cat. # 1007

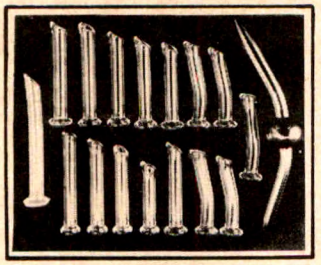
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*L. T. JONES, M.D. DACRYOCYSTORHINOSTOMY, AMERICAN JOURNAL OF OPHTHALMOLOGY, VOLUME 59, NO. 5, MAY 1965.

CATARACT WORKSHOP

Phakoemulsification, Lens Implant, Vitrectomy and other modalities will be key subjects of a special workshop on **Cataract Surgery** at the 1976 AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY annual meeting (Feb. 29-Mar. 5, Americana Hotel, Bal Harbour/Miami Beach, Florida). The workshop will be presented in five afternoon sessions by Drs. Charles Kelman, Jack Hartstein, Norman Jaffe, Stanley Becker, Harvey Lincoff, Antonio Gasset and others.

The meeting will feature other workshops in Microsurgery and Stereoscopic Studies of the Anterior Segment; Contact Lenses in Aphakia and Corneal Diseases; Gonioscopy; Glaucoma; and Refraction.

More than 50 leading ophthalmologists will participate with the following chairmen: Cataract, David Paton; Retinal Diseases, Harvey Lincoff; Glaucoma, H. Saul Sugar; Cornea/External Diseases, Claes Dohlman; Pediatric Ophthalmology, Donelson Manley; Corneal Surgery, Herbert Kaufman; and Oculoplastic Surgery, Pierre Guibor. Jules Francois is Chairman of the entire meeting. Registrants earn 40 or more credit hours in CME.

Write: AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY
30 North Michigan Avenue, Chicago, Illinois 60602

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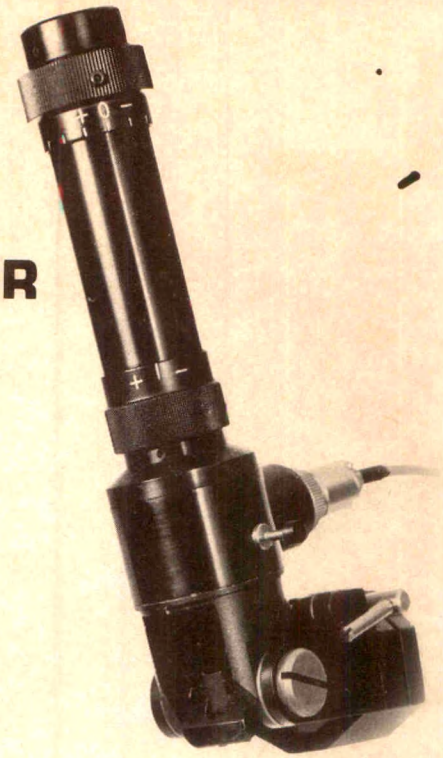
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Tuition is $675.00. For further information and application forms, please write to J. W. Bettman, M.D., Division of Ophthalmology, A-227, Stanford Medical Center, Stanford, California 94305.

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The 1976 annual meeting and scientific assembly of the American Society of Contemporary Ophthalmology will be held February 29 through March 5 at the Americana Hotel, Bal Harbour (Miami Beach), Florida.

Under the direction of Dr. Jules Francois, Chairman; Dr. Herbert Kaufman, President; and Dr. Claes Dohlman, President-Elect, more than 50 leading ophthalmologists will hold seminars presenting the latest information in clinical ophthalmology and workshops in New Techniques of Cataract Surgery and Lens Implants, Microsurgery of the Eye, Oculoplastic Surgery, Cornea, Glaucoma, Retina, Strabismus, Pediatric Ophthalmology, Contact Lenses, Refraction, Gonioscopy, Stereoscopic Studies of the Anterior Segment—and other subjects.

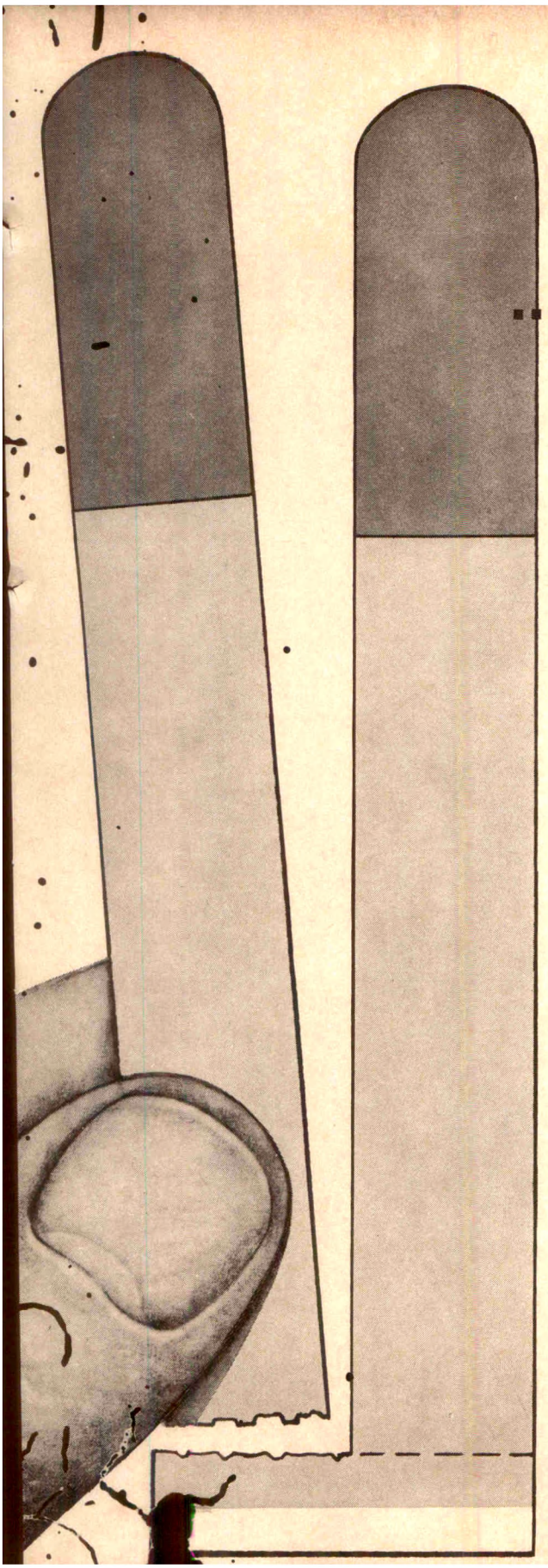
Registrants will earn up to 40 CME credit hours acceptable in Category 1 for the AMA Physician's Recognition Award and for the ASCO Certificate of Advanced Studies in Ophthalmology.

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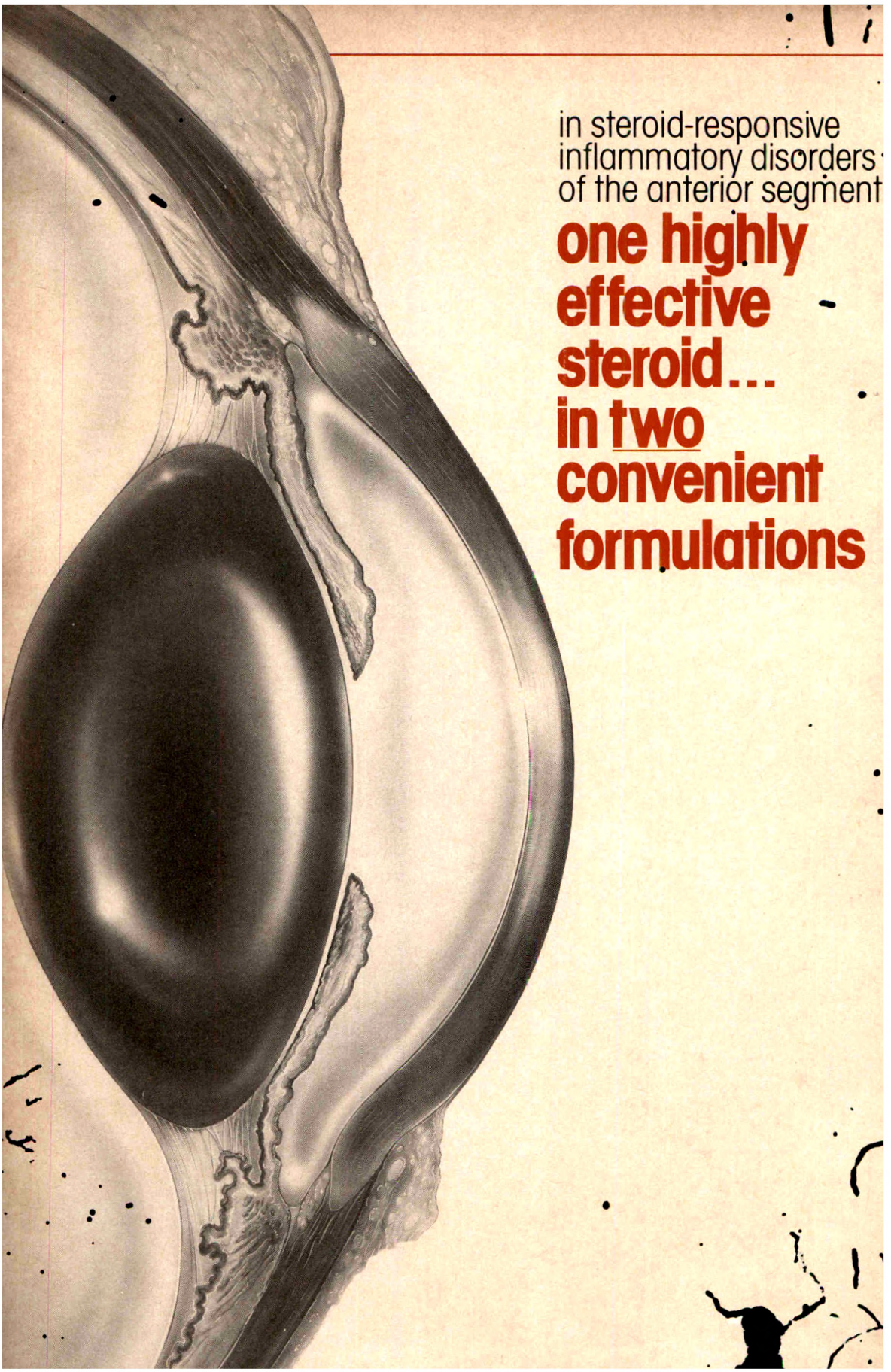
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- melts below body temperature: medication spreads evenly over the entire eye preventing "blink-out"
- useful at bedtime or under a patch (to allow for individual patient needs)
- particularly useful when prolonged contact of steroid medication is indicated

Contraindications: Acute superficial herpes simplex keratitis.

Fungal diseases of ocular or auricular structures.

Vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva.

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Hypersensitivity to a component of this medication.

Perforation of a drum membrane.

Warnings: Employment of steroid medication in the treatment of stromal herpes simplex requires great caution; frequent slit-lamp microscopy is mandatory.

Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from pathogens liberated from ocular tissues.

In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids.

Acute purulent untreated infection of the eye or ear may be masked or activity enhanced by the presence of steroid medication.

Usage in Pregnancy—Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated.

Precautions: As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.

Intraocular pressure should be checked frequently.

Adverse Reactions: Glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex liberated from ocular tissues, perforation of the globe.

Viral and fungal infections of the cornea may be exacerbated by the application of steroids.

Rarely, stinging or burning may occur.

How Supplied: Sterile ophthalmic solution in 2.5-ml and 5-ml glass bottles with dropper assembly and in 5-ml OCUMETER® ophthalmic dispensers, containing per milliliter of buffered solution: dexamethasone sodium phosphate equivalent to 1 mg (0.1%) dexamethasone phosphate; creatinine, sodium citrate, sodium borate, polysorbate 80, disodium edetate in the OCUMETER, sodium hydroxide to adjust pH in glass bottles, hydrochloric acid to adjust pH in plastic dispensers, water for injection, and sodium bisulfite, phenylethanol, and benzalkonium chloride added as preservatives. Ophthalmic ointment in 3.5-g tubes, containing per gram: dexamethasone sodium phosphate equivalent to 0.5 mg (0.05%) dexamethasone phosphate; white petrolatum and mineral oil.

For more detailed information, consult your MSD representative or see full prescribing information.

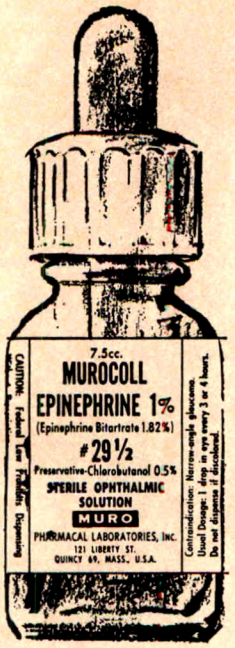
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- Aids in breaking posterior synechiae in uveitis.

Murocoll Epinephrine 1% (as Bitartrate 1.82%) with Chlorobutanol 0.5% as a preservative and bacteriostatic agent is also available as Murocoll Epinephrine 2% (as Bitartrate 3.64%), Product #29.

Both solutions also have Sodium Bisulfite as preservative; Sodium Chloride and distilled water as inactive ingredients.

Above solutions are contraindicated in narrow angle glaucoma.
Use with caution in presence of hypertension.

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Otolaryngology Speakers:

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THE PALO ALTO RETINAL GROUP
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THE PALO ALTO RETINAL RESEARCH FOUNDATION
announce

Palo Alto Course in Diagnosis and Management of Retinal Disease

13th Course—January 22, 23, 24, 1976
14th Course—July 22, 23, 24, 1976

Palo Alto Retinal Group Faculty:
H. Christian Zweng, M.D.
Robert L. Jack, M.D.
Hunter L. Little, M.D.

Guest Lecturers:
Lloyd M. Aiello, M.D. Francis L'Esperance, Jr., M.D.
Arnall Patz, M.D. Arthur Vassiliadis, Ph.D.
Howard Schatz, M.D.

This course is designed to give up-to-date information on retinal diseases.

. . . to give a basic knowledge of retinal fluorescein angiography.
. . . to give an understanding of how lasers work and of currently available argon laser photocoagulators.
. . . to give an understanding of "quantitative" photocoagulation.
. . . to give current indications for, contraindications to, and complications of argon laser photocoagulation.
. . . to give demonstrations of actual use of argon laser photocoagulation.

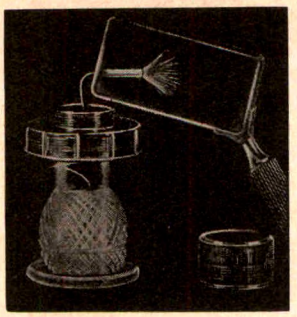
Registration Fee: $350.00 (includes lectures, 2 luncheons, cocktail party and banquet).

Enrollment is limited and advance registration is required.

For application forms and further information, write to:
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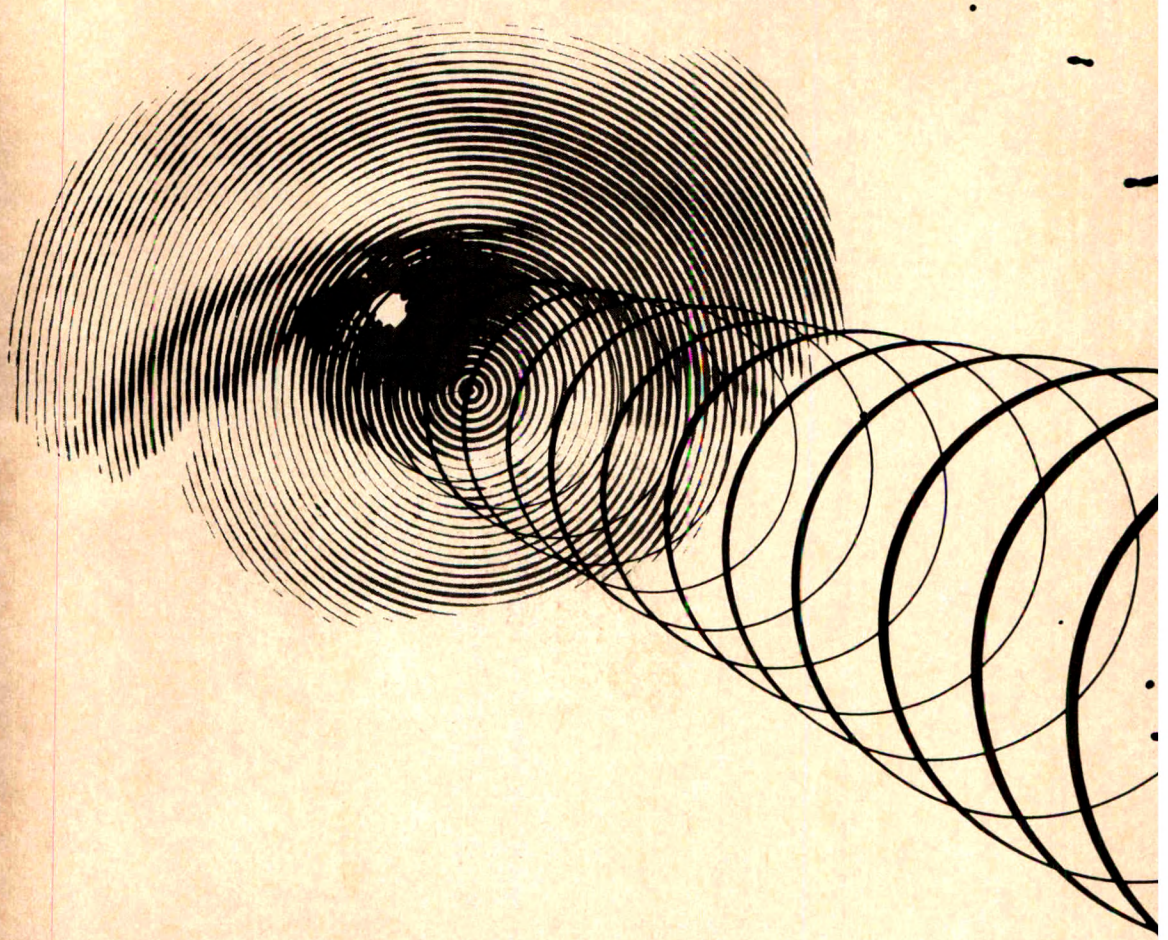
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This area is the site of the prim
pathologic changes which a
responsible for glaucoma and th
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procedures for treatment of the diseas

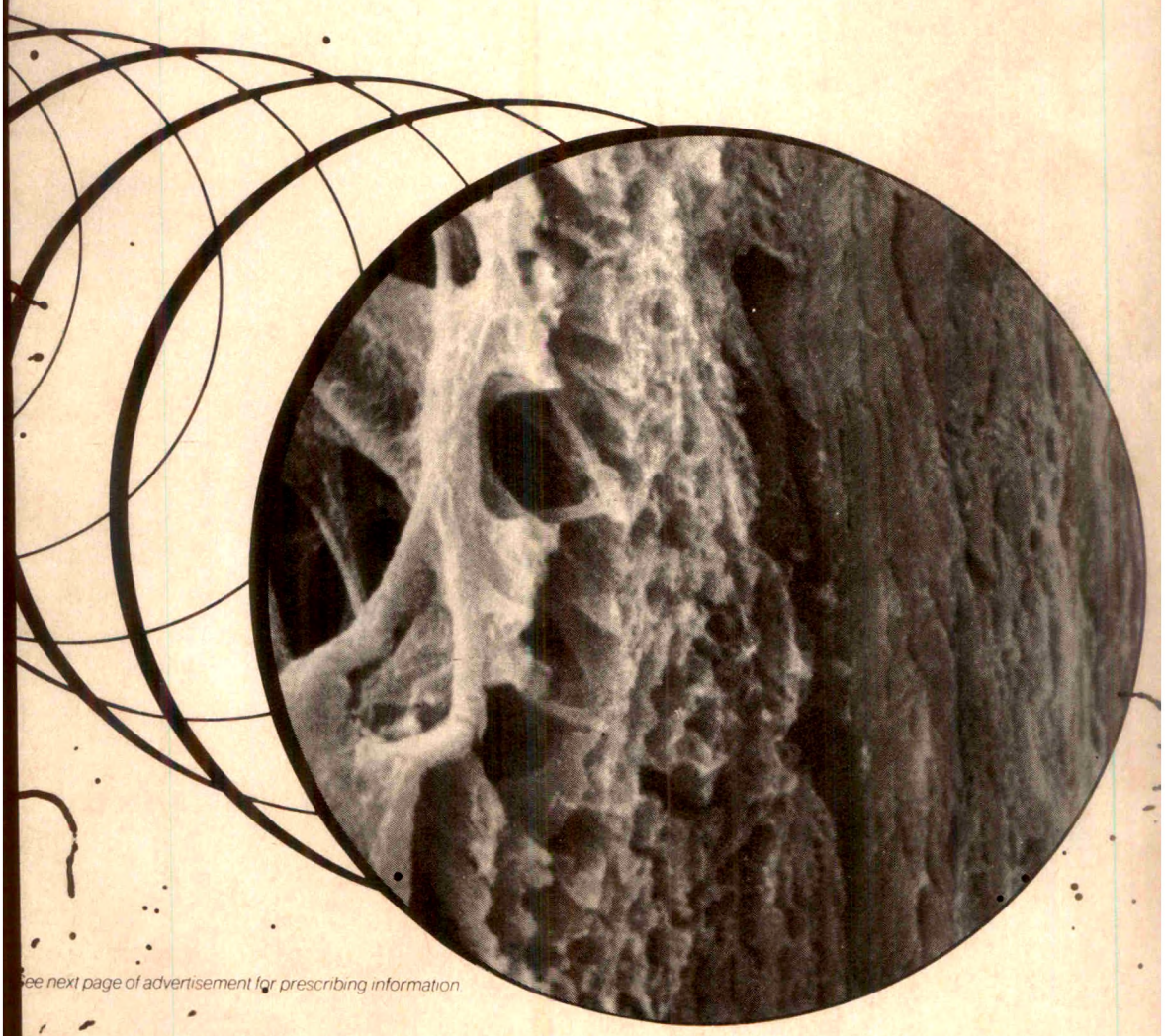
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in the management of chronic simple (open-angle) glaucoma or glaucoma secondary to aphakia

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PHOSPHOLINE IODIDE® (echothiophate iodide)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia—Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

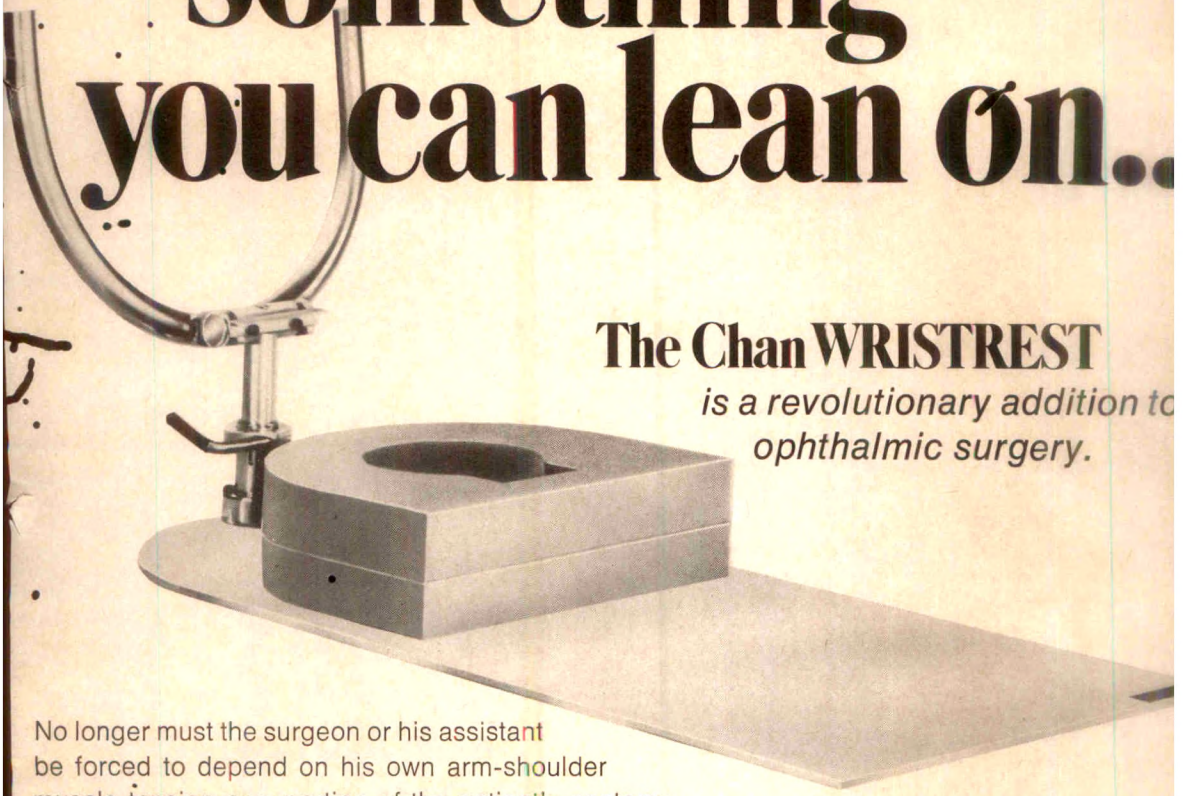
6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.]

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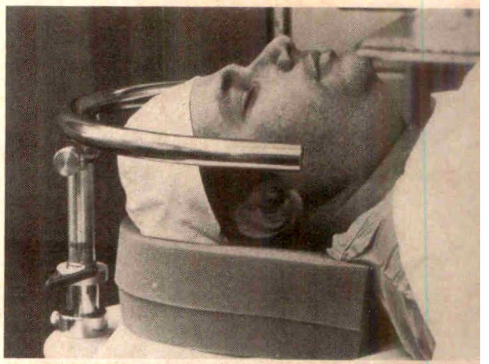


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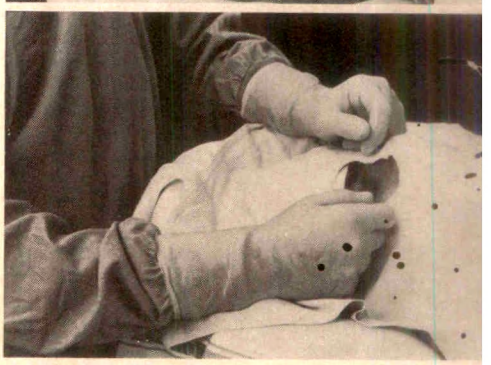
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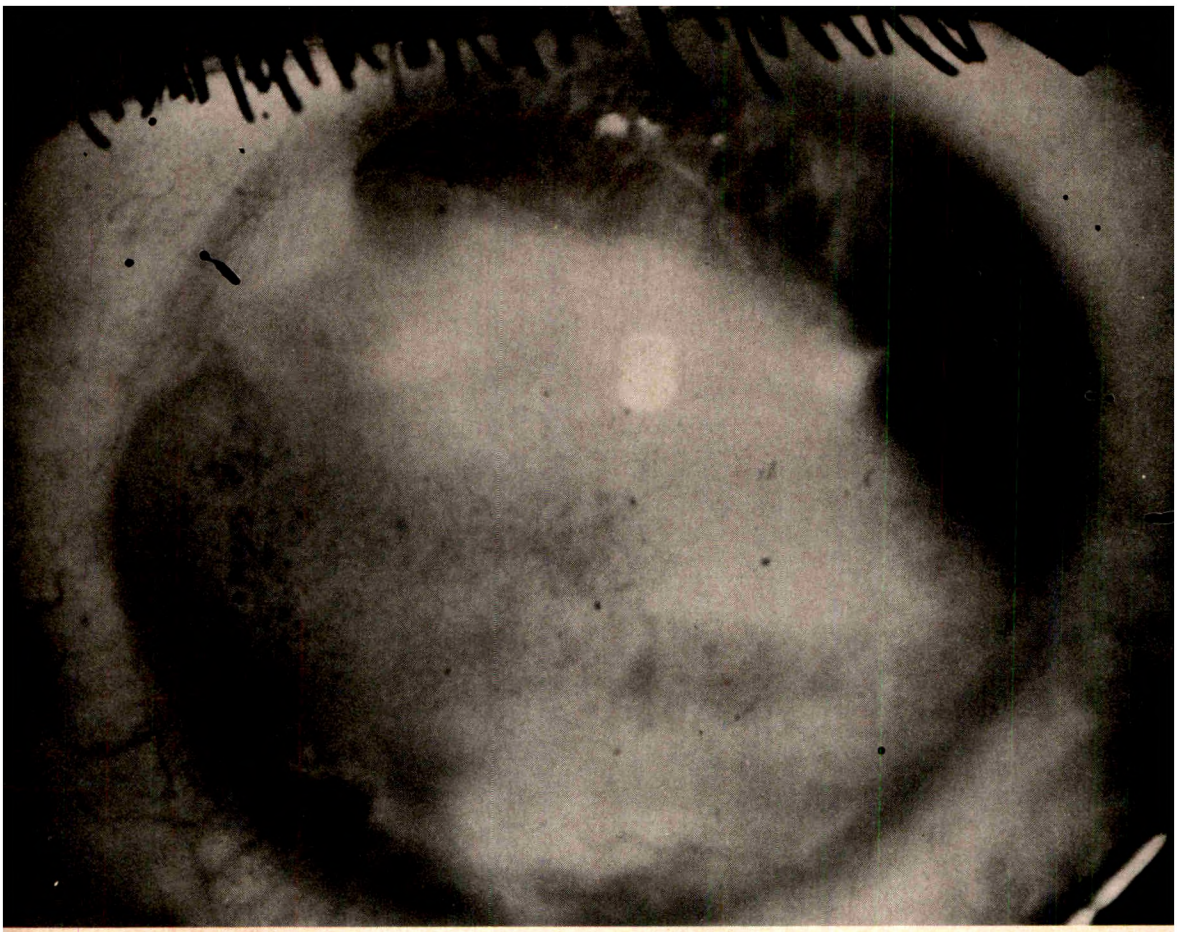


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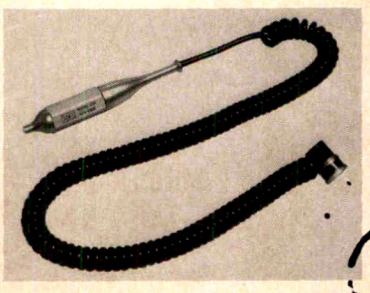


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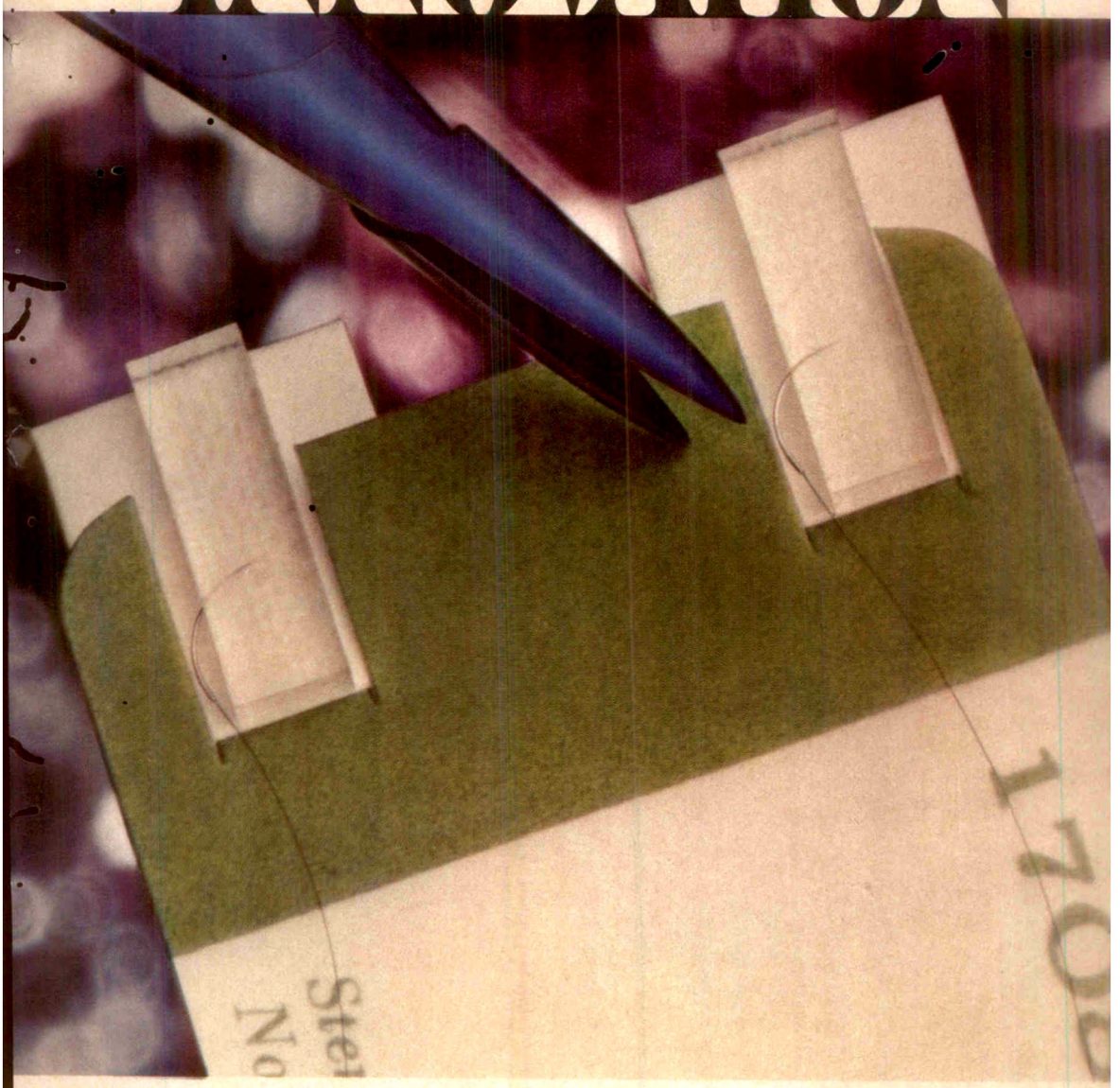


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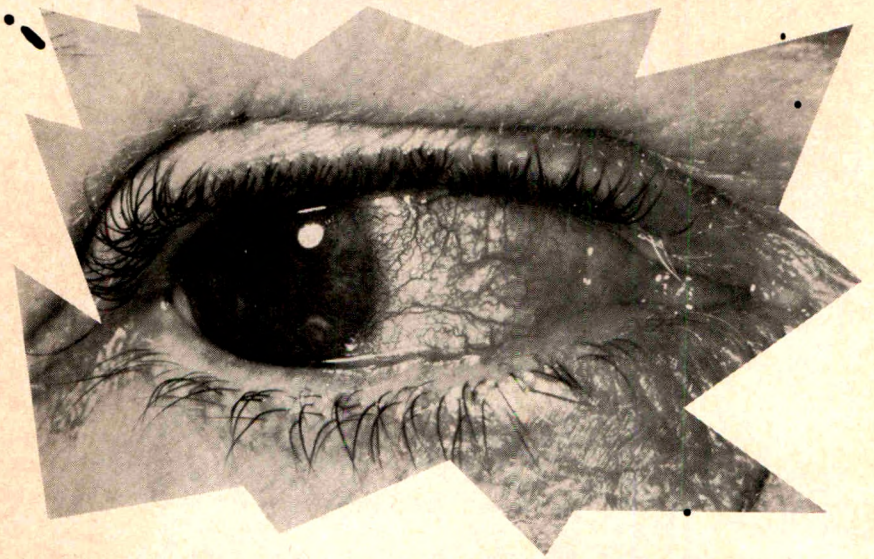


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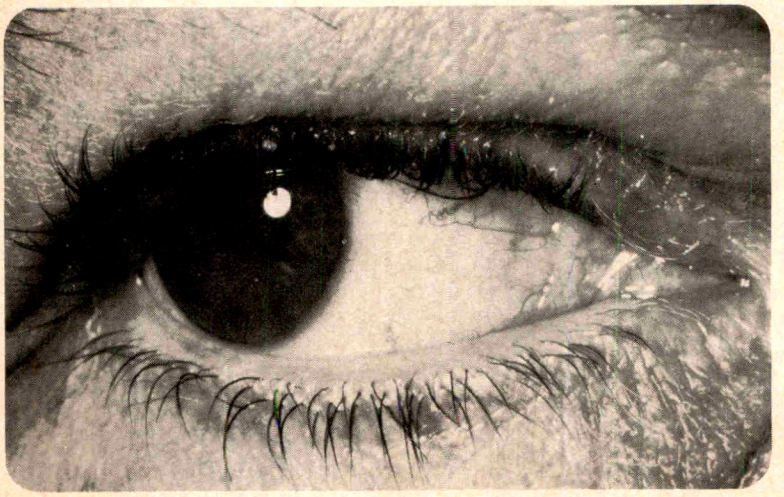
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DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

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INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

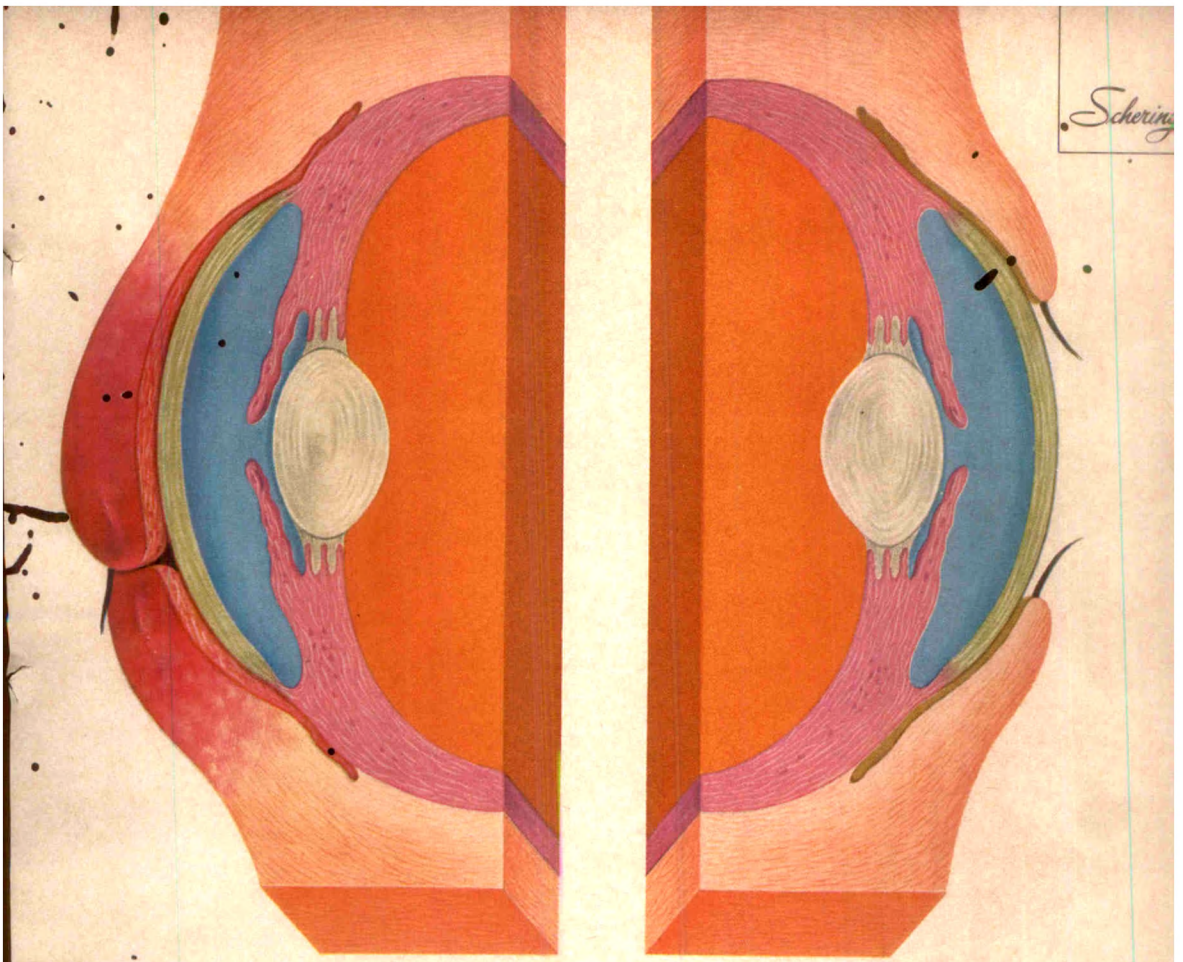
HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube, boxes of one and six. Store away from heat.

NOVEMBER 1973

For complete details, consult package insert or literature available from your Schering Representative; or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Schering Corporation



Schering

The eye opener in bacterial conjunctivitis

■ Clears up conjunctivitis and other infections of the external eye and adnexa due to susceptible strains of gram-negative *H. influenzae, E. coli, K. pneumoniae, M. lacunata, Enterobacter aerogenes* (formerly *Aerobacter*), *H. aegyptius* and *Neisseria* sp., including *N. gonorrhoeae.*

■ Clears up conjunctivitis and other infections of the external eye and adnexa due to susceptible strains of gram-positive staphylococci and streptococci, including *D. pneumoniae.*

■ Clears up infections* of the external eye and adnexa due to problem organisms: *P. aeruginosa* (certain strains) and *Proteus* sp. (sensitive strains, both indole-positive and -negative).

■ Clears up infections* of the external eye and adnexa generally without sensitivity reactions and irritation. No significant organism resistance to date. This may occur in the future. Resistance to gentamicin has been produced (with difficulty) *in vitro* by repeated exposures.

Clears up external eye infections* caused by a wide range of ocular pathogens

*due to susceptible organisms.

WIDE GRAM-NEGATIVE SPECTRUM AND GRAM-POSITIVE ACTIVITY

GARAMYCIN® OPHTHALMIC

brand of gentamicin sulfate, U.S.P.

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin

Solution-Sterile
Ointment-Sterile

Peter can't play any position.



Accommodative esotropia may prevent a child from developing the skills necessary for competitive sports. Lack of binocular single vision may affect school work as well as play...and negative cosmetic effects may alter peer relationships.

Phospholine Iodide (echothiophate iodide) may be able to change the lineup.

Diagnosis... To help determine if there is an accommodative basis for the esotropia, one drop of PHOSPHOLINE IODIDE 0.125% may be instilled daily in each eye, prior to retiring, for two or three weeks.

Treatment... If there is a significant accommodative factor present, the continued use of PHOSPHOLINE IODIDE alone is often sufficient for treatment, as long as the drug is well tolerated. PHOSPHOLINE IODIDE acts by altering the accommodative convergence/accommodation relationship in a favorable way, so that near vision is obtained with less accommodative effort, and fusion can be maintained.

If surgery is necessary, postoperative use of PHOSPHOLINE IODIDE may help correct a residual deviation.

Phospholine Iodide®

(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)

in the diagnosis and treatment of accommodative esotropia

BRIEF SUMMARY

(For full prescribing information, see package circular.)

PHOSPHOLINE IODIDE®

(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)

PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.

Indications: 1. Glaucoma—Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.

Accommodative esotropia—Concomitant esotropias with a significant accommodative component.

Contraindications: 1. Active uveal inflammation.

2. Most cases of angle closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.

Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or in the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.

Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.

Adverse Reactions: 1. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

2. Retinal detachment has been reported occasionally.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under anticholinesterase therapy have been reported; routine examinations should accompany prolonged use.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.

Overdosage: Antidotes are atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg. per kg. intravenously; artificial respiration should be given if necessary.

How Supplied: Four potencies are available. 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

Diamox® preserves the panorama

Acetazolamide

DIAMOX retards loss of peripheral vision in glaucoma* by reducing secretion of aqueous humor and thus intraocular pressure.



*In chronic simple (open-angle) glaucoma and secondary glaucoma.

Diamox–all forms

Acetazolamide

Before prescribing, consult package insert.

Indications: Tablets and Parenteral only: For adjunctive treatment of: edema due to congestive heart failure; drug-induced edema; centrencephalic epilepsies (petit mal, unlocalized seizures). **All forms:** Chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Contraindications: When sodium and/or potassium serum levels are depressed, in marked kidney and liver disease or dysfunction, suprarenal gland failure and hyperchloremic acidosis. Long-term use in chronic noncongestive angle closure glaucoma.

Warning: Although teratogenic and embryocidal effects demonstrated in mice at more than ten times the equivalent therapeutic doses have not been evidenced in humans, do not use DIAMOX in pregnancy, especially during the first trimester, unless expected benefits outweigh these potential

Precautions: Increasing the dose may increase drowsiness and paresthesia and decrease diuresis. Adverse reactions common to all sulfonamide derivatives may occur: fever, rash, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, agranulocytosis. Early detection is advised and if such occur, discontinue drug and institute appropriate therapy.

Adverse Reactions: Short-term therapy: (minimal) paresthesias, particularly a "tingling" feeling in the extremities; some loss of appetite, polyuria, drowsiness, confusion. Long-term therapy: An acidotic state may supervene usually corrected by bicarbonate. Transient myopia.

Other: (occasional) urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, convulsions.

Diamox® Sequels® add convenience to control

· **Acetazolamide Sustained Release Capsules** 500 mg. b.i.d.



Diamox® Sequels® Offer:

Simple b.i.d. Schedule

Once-in-the-morning, once-in-the-evening regimen reduces likelihood of skipped doses.

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Sustained release of medication achieves continuous drug action to effectively decrease secretion of aqueous humor.

Smooth, Round-the-Clock Control

Continuous drug action helps even out erratic peak-pressure periods.

And DIAMOX Acetazolamide does not interfere with the activity of miotics or other topicals. In fact, it often provides a complementary effect when used with miotics.

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Acetazolamide
125 mg./250 mg. Tablets

Diamox Sequels®
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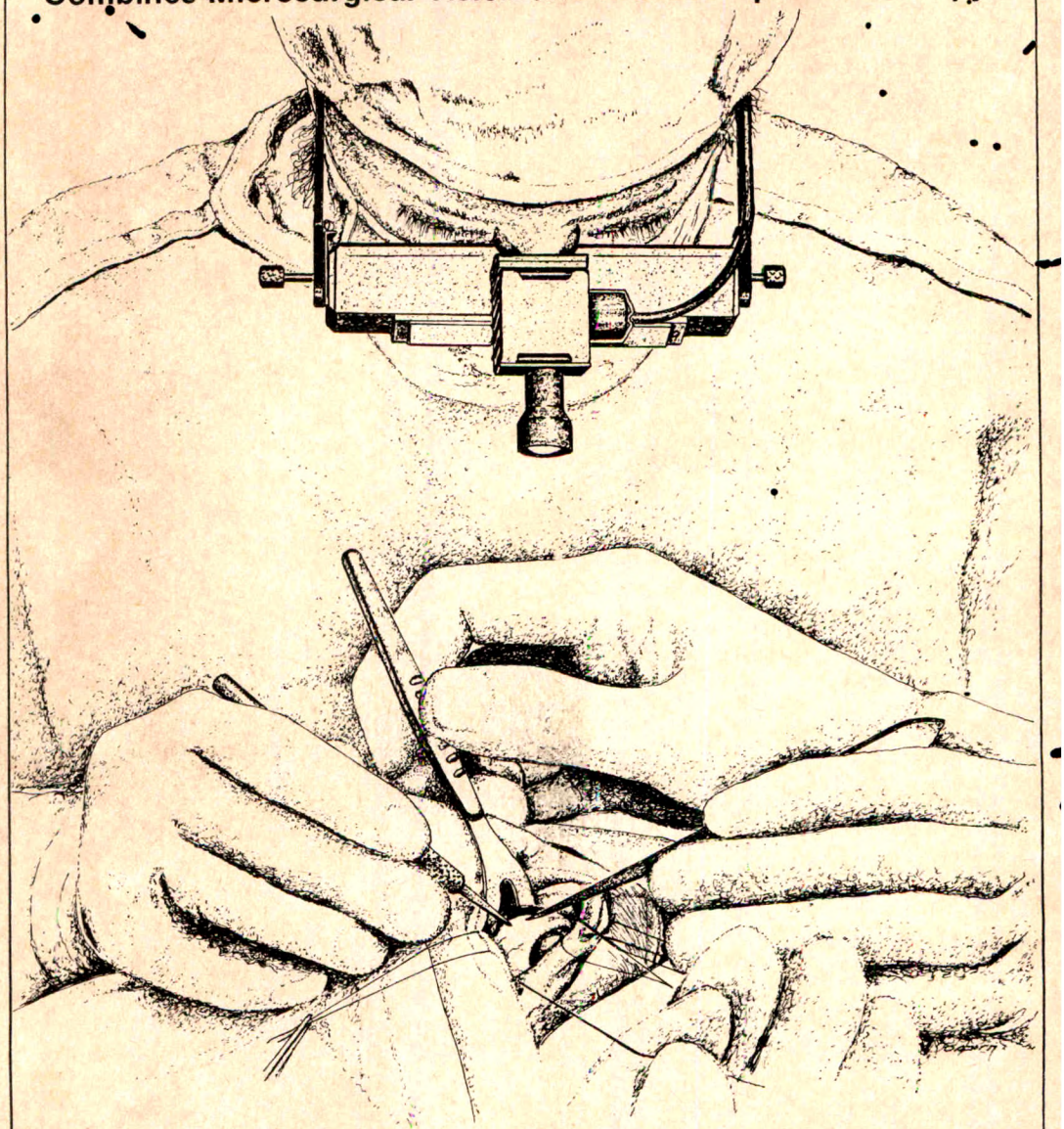
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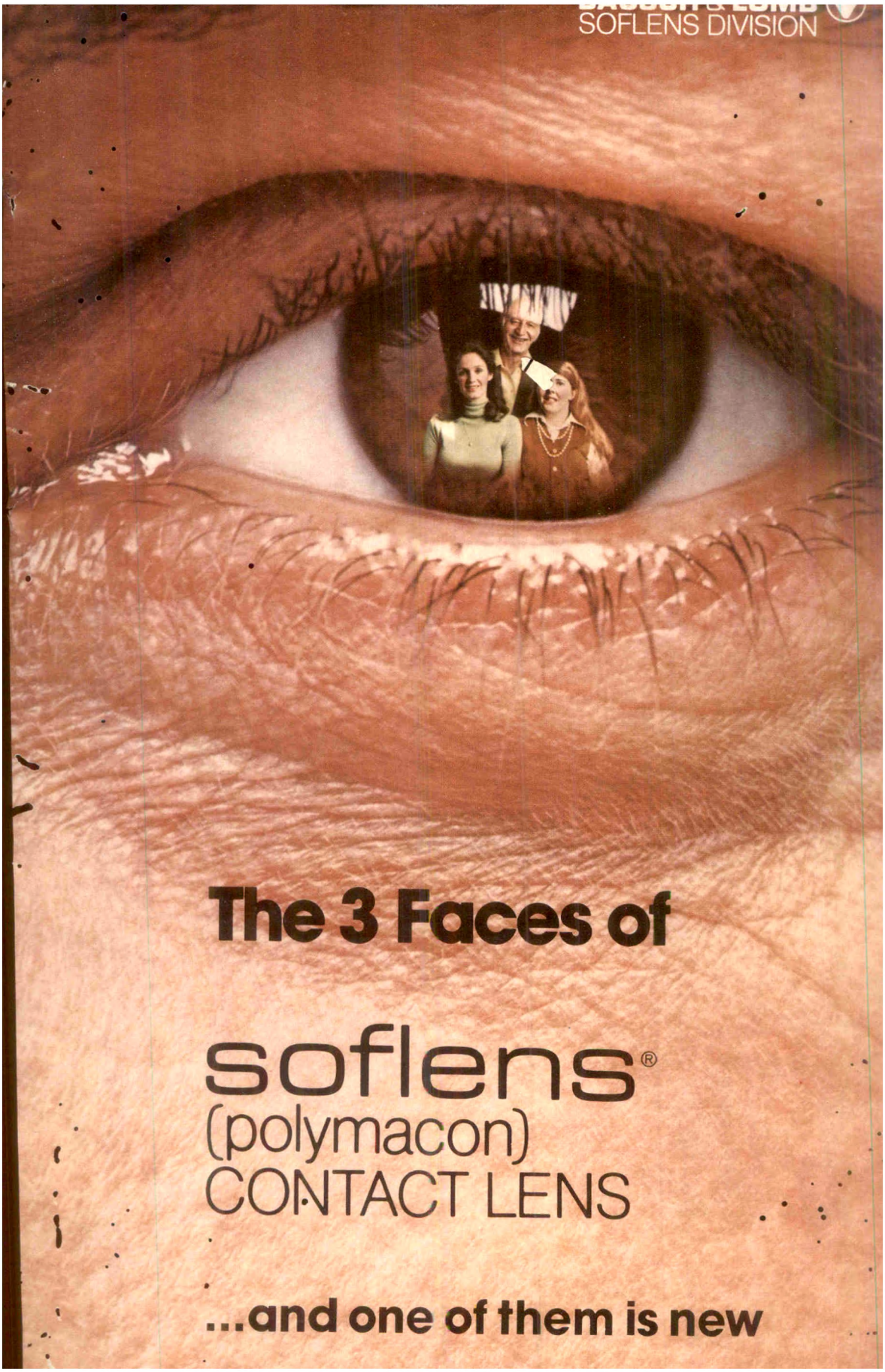


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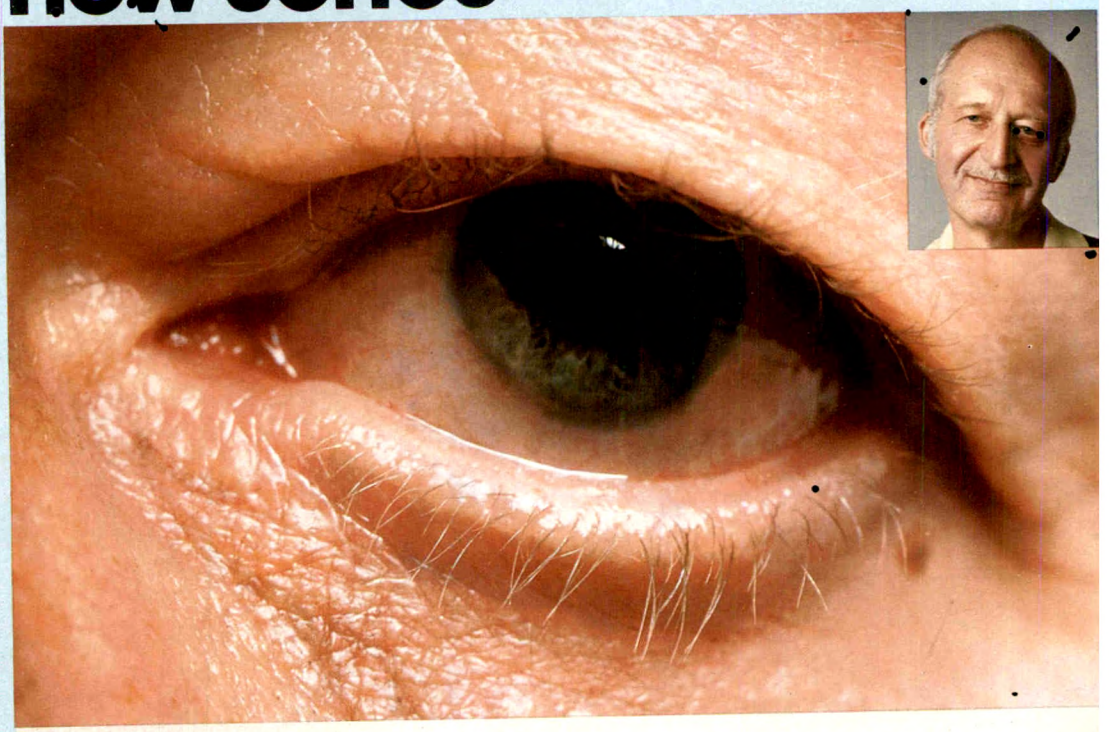
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SOFLENS DIVISION
The 3 Faces of
soflens®
(polymacon)
CONTACT LENS
...and one of them is new

Introducing a new series



For the Face of Aphakia

The high-plus F3 series

The new high-plus F3 series SOFLENS® (polymacon) Contact Lens is a flatter-fitting high-plus lenticular lens. It has uniform center thickness throughout the power range, which allows for a more predictable fit. The new 13.6mm high-plus F3 series allows less decentration and is available in powers ranging from +10.00D to +20.00D in half-diopter steps. For patients who need a steeper-fitting lens, the high-plus N series is available.

Now, more aphakic patients than ever before may benefit from wearing SOFLENS Contact Lenses.

*Data on file, Bausch & Lomb SOFLENS Division.

See next page for a brief summary of the prescribing information.



For the Face of Therapeutics

For the patient with painful bullous keratopathy, SOFLENS Contact Lens may provide effective symptomatic relief. Recent clinical studies show that the pain of the condition was relieved in almost eight out of every ten patients.*

For the Face of Vision Correction

For patients who want the "natural look" of contact lenses, the SOFLENS® (polymacon) Contact Lens is available in a wide variety of powers and lens curvatures in B, F, J, N and C series. Comfort, good-to-excellent visual acuity, freedom from spectacles and ease of adaptation are the reasons most often cited by patients for their preference of SOFLENS Contact Lenses.



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(polymacon)
CONTACT LENS

From

BAUSCH & LOMB
SOFLENS DIVISION



soflens®
(polymacon) CONTACT LENS

VISION CORRECTION AND THERAPEUTIC USE BRIEF SUMMARY
(for full prescribing information, see product labeling)

DESCRIPTION: A hemispherical flexible shell which covers the cornea and may cover a portion of the adjacent sclera.

ACTIONS: When placed on the human cornea, the hydrated lens acts as a refracting medium to compensate spherical ametropias and as a pain reliever by providing a well-tolerated barrier between the exposed corneal nerves and the lids.

INDICATIONS: For vision correction use in persons with non-diseased eyes and in aphakia; may be useful in the treatment and management of painful bullous keratopathy.

CONTRAINDICATIONS: Contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia, aphakia, and painful bullous keratopathy.

WARNINGS: Abrasions and Infections—If a lens becomes less comfortable, it should be removed immediately, and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrent with lens wear, the lens should be removed immediately and a physician consulted. Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses.

Aphakic Patients—Aphakic patients should not be fitted with the lenses during the post-operative period until, in the opinion of the surgeon, the eye has healed completely.

Lens Sanitation and Handling—Persons who require only vision correction and who would not, or could not, adhere to the recommended daily sanitary care of the lenses or who are unable to place and remove the lenses should not be provided with them. Failure to follow handling and sanitation instructions could lead to serious eye infections which might result in corneal ulcers.

Malfunction and rusting of the metal interior of the Aseptor®—Patient Unit as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure.

Medicants and Eye Drops—No solutions, including conventional contact lens solutions, other than normal saline, and the solution made from the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets are to be used on a SOFLENS® (polymacon) Contact Lens when the lens is off the eye.

Vision Correction Use: No ophthalmic solutions or medicants, including conventional contact lens solutions and eye drops, should be used by lens wearers prior to placement or while the lens is in place on the eye.

Therapeutic Use: The patient should be instructed to use only eye drops prescribed by the physician when the lens is on the eye. Medication with preservatives may be used when indicated in the usual dosage regimens. Repeated use of epinephrine drops, as well as a single fluorescein instillation, will cause discoloration of the lens. Deposits, which frequently occur on the lens with continuous wear, may cause discomfort and necessitate replacement as often as every two or three months.

Wearing Restrictions—Lenses used only for vision correction should be removed before sleeping or swimming. The lenses should not be used in the presence of noxious and irritating vapors. Safety in pregnancy has not been substantiated. Insufficient lacrimal secretions or hypoesthesia may be restricting factors to the wearing of soft contact lenses.

PRECAUTIONS: Placement and Removal—Lenses worn for therapeutic purposes should be applied and removed only by the physician. However, all patients should be instructed in the techniques of placing and removing a lens so they can do so should it become necessary.

When the lens is used for the treatment of painful bullous keratopathy, it is to be worn continuously, for 24 hours a day, following the initial application. The patient should be followed closely during the initial stages of treatment. The lens should be comfortable and the pain of bullous keratopathy should be relieved almost immediately. If the lens is not comfortable and pain persists, another lens should be tried for appropriate fit.

Daily placement and removal of the lens by the patient may be permitted. However, if daily removal increases the risk of additional damage to the already compromised corneal epithelium and when the degree of pain relief is significant during the time the lens is worn, continuous wear should be employed.

Storage—Lenses must be stored ONLY in normal saline solution. If left exposed to air, the lenses dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in normal saline solution until it returns to its soft, pliable state which may take as long as forty minutes.

Fresh normal saline must be prepared for cleaning and storing the lenses. This must be done daily when the lenses are worn for vision correction purposes. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The one-ounce squeeze bottle is intended for preparation of normal saline only. As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used as it will have been disinfected.

Hygiene—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses.

Cosmetics, lotions, soaps, and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

SL 1265 November, 1975

One lens for three indications

aphakia
vision correction
painful bullous keratopathy

Handling—A lens may be damaged by nicking or tearing if care is not exercised during placement on or removal from the eye, replacing or removing it from the carrying case or in the cleaning process. Lenses must be placed very carefully in the carrying case to avoid damaging the edges of the lenses.

Disinfecting—Fresh normal saline must be prepared daily. After removal from the eye, the lens must be irrigated with saline and rubbed gently to remove mucus and film from the lens surface. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The causes and nature of deposits formed on the surface of some lenses have not been completely evaluated. However, some coatings are known to be proteinaceous and others may be oily or greasy film from extraneous agents, such as hair spray or other cosmetics, or from the patient's own lacrimal secretions. Many wearers experience little or no difficulty with such deposits. However, occasionally a wearer, who tends to secrete unusually large amounts of mucus in the lacrimal fluid, may experience a build-up of these deposits within a relatively few weeks, despite adequate cleaning measures. If surface accumulations of non-removable materials persist, professional care should be obtained promptly.

The SOFLENS Carrying Case should be washed at least once a week with hot water and then rinsed thoroughly with distilled water. Soap or other cleaners should never be used to clean the carrying case.

In order to remove protein deposits which may form on the lenses, wearers should use the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets according to the directions for use which accompany the tablets. To prevent the formation of the protein deposits, patients should use the SOFLENS Enzymatic Contact Lens Cleaning Tablets once a week or as directed by the practitioner.

Disinfecting with the SOFLENS® Aseptor®—Patient Unit is necessary to kill microorganisms. If a SOFLENS Aseptor—Patient Unit is not available, the lenses may be disinfected by boiling them in their carrying case in a pan of water for 15 minutes. When this boiling method of disinfection is used, the lenses can be damaged if the boiling water is allowed to completely evaporate. The carrying case must always be tightly closed before disinfecting to prevent leakage of the saline from the case and subsequent dehydration of the lenses.

Fluorescein—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with sterile normal saline solution and wait at least one hour before replacing the lenses. Earlier replacement may cause the lenses to absorb residual fluorescein.

ADVERSE REACTIONS: Infiltrates, neovascularization, and corneal ulcers have been reported in some wearers of the lenses for therapeutic use.

Serious corneal damage may result from wearing a lens which has been soaked in conventional contact lens solution.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

A lens adheres very rarely to an eye as a result of sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema, as manifested by symptoms such as rainbows, halos around lights, or foggy vision, may occur in less than 5% of lens wearers. If these symptoms occur, the lenses should be removed and professional consultation obtained.

Excessive tearing, unusual eye secretions, and photophobia are not normal. If these symptoms occur, the patient should be examined to determine their cause.

A faint blue haze, believed to be located in Descemet's membrane, has been reported in the Spokane, Washington, area in approximately 26 wearers with otherwise normal eyes. As yet, the cause is unknown and the phenomenon has not been found elsewhere. The wearers report no subjective symptoms and there is no detectable effect on their visual acuity.

Neovascularization of the cornea, which may require discontinuation of the lens, has been observed in some aphakic patients fitted with SOFLENS® (polymacon) Contact Lens, and in such instances medical consultation should be obtained.

HOW SUPPLIED: Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the manufacturing lot number of the lens and the dioptric power (black for plus power lenses; red for minus; gold for plano).

Caution: Federal Law Prohibits Dispensing Without a Prescription.

The SOFLENS® Care Kit is available for lens disinfecting, cleaning, and storage, consisting of the following:

Lensgard™ Carrying Case	Cat. #140307
SOFLENS® Aseptor®—Patient Unit	Cat. #140302
SOFLENS™ Enzymatic Contact Lens Cleaning Tablets	Cat. #140310
SOFLENS® Squeeze Bottle	Cat. #140304
SOFLENS® Salt Tablets	Cat. #140305
SOFLENS® Patient Instruction Book	Cat. #140300.100

SOFLENS Enzymatic Contact Lens Cleaning Tablets are also supplied in refill packages of:
24 Tablets Cat. #140395 48 Tablets Cat. #140396

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Sunday, February 8, 1976, 9 a.m.-5 p.m.
Hyatt Regency Hotel, San Francisco

Symposium on the Cornea

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Herpetic Keratitis

Trauma Management

Innovative Microsurgical Techniques

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Bullous Keratopathy

Complications of Cataract and Vitreous Surgery

Soft Contacts: Complications and Prospects

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George O. Waring, MD,
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Enclosed is my check for $25 payable to the CMA Section on Ophthalmology

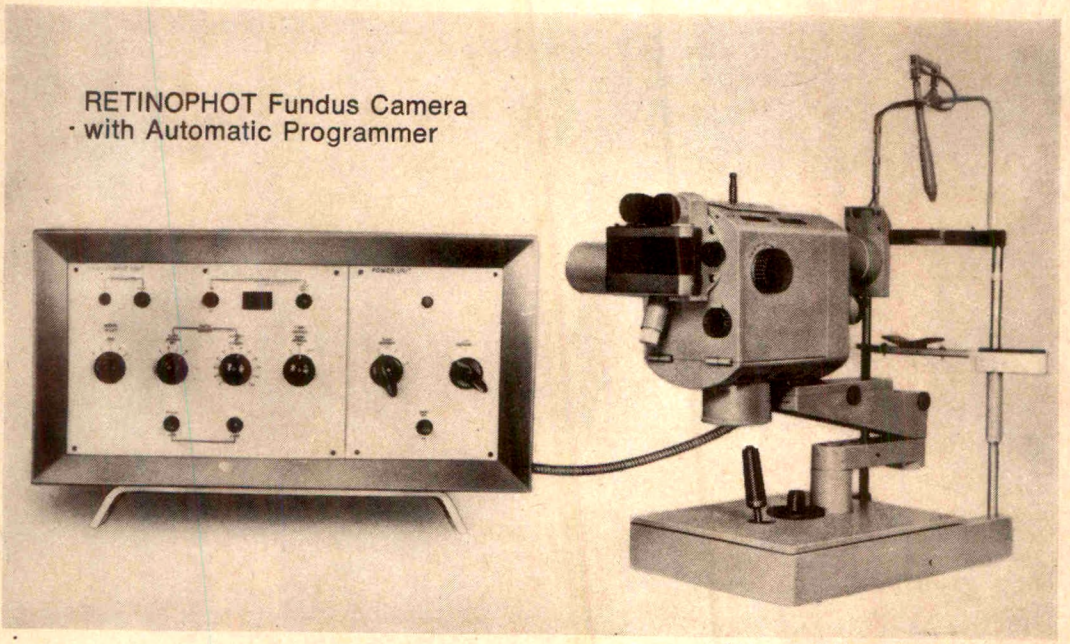
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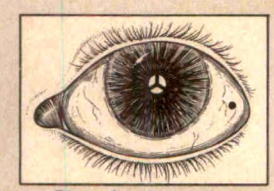
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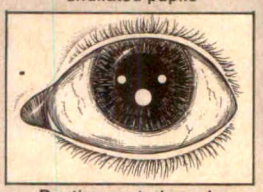
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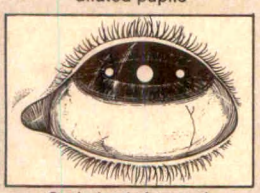
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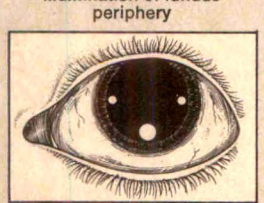
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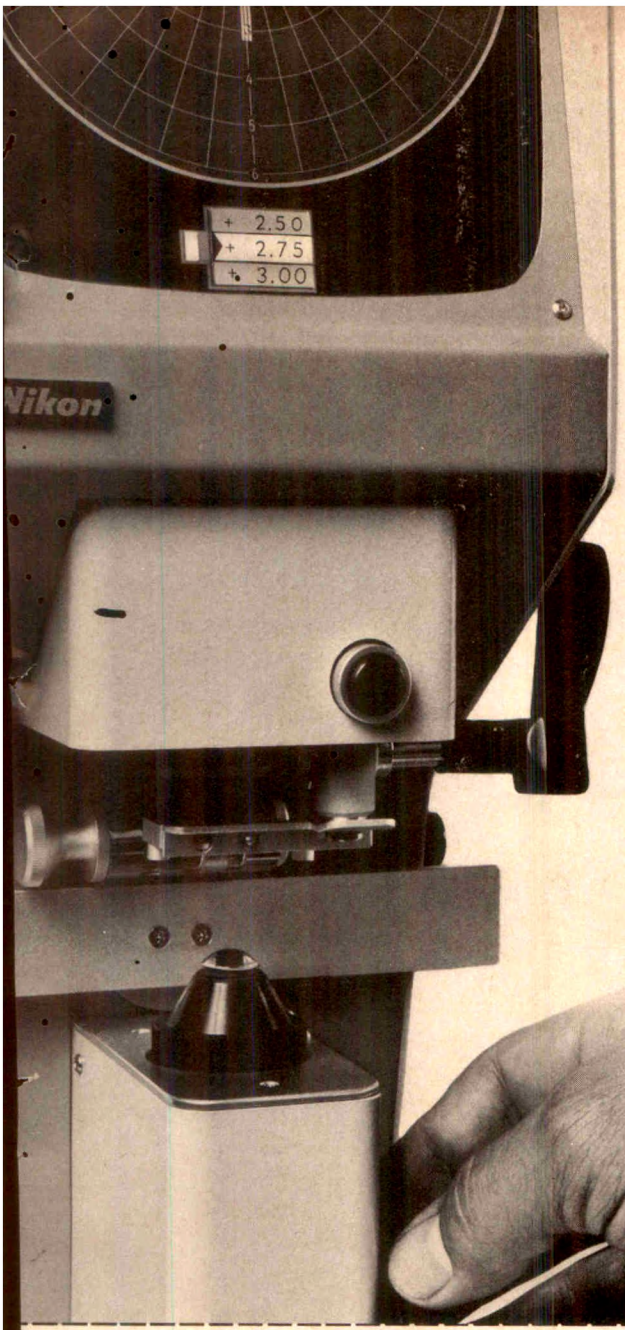
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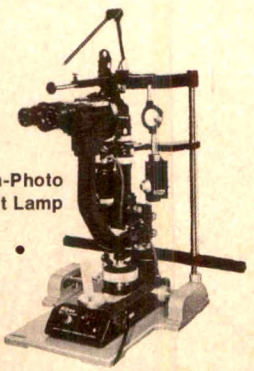
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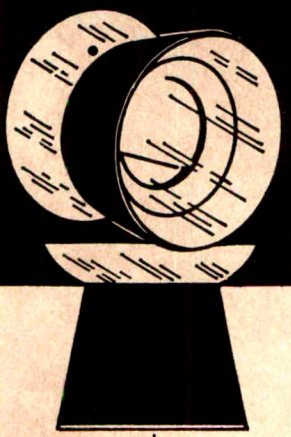
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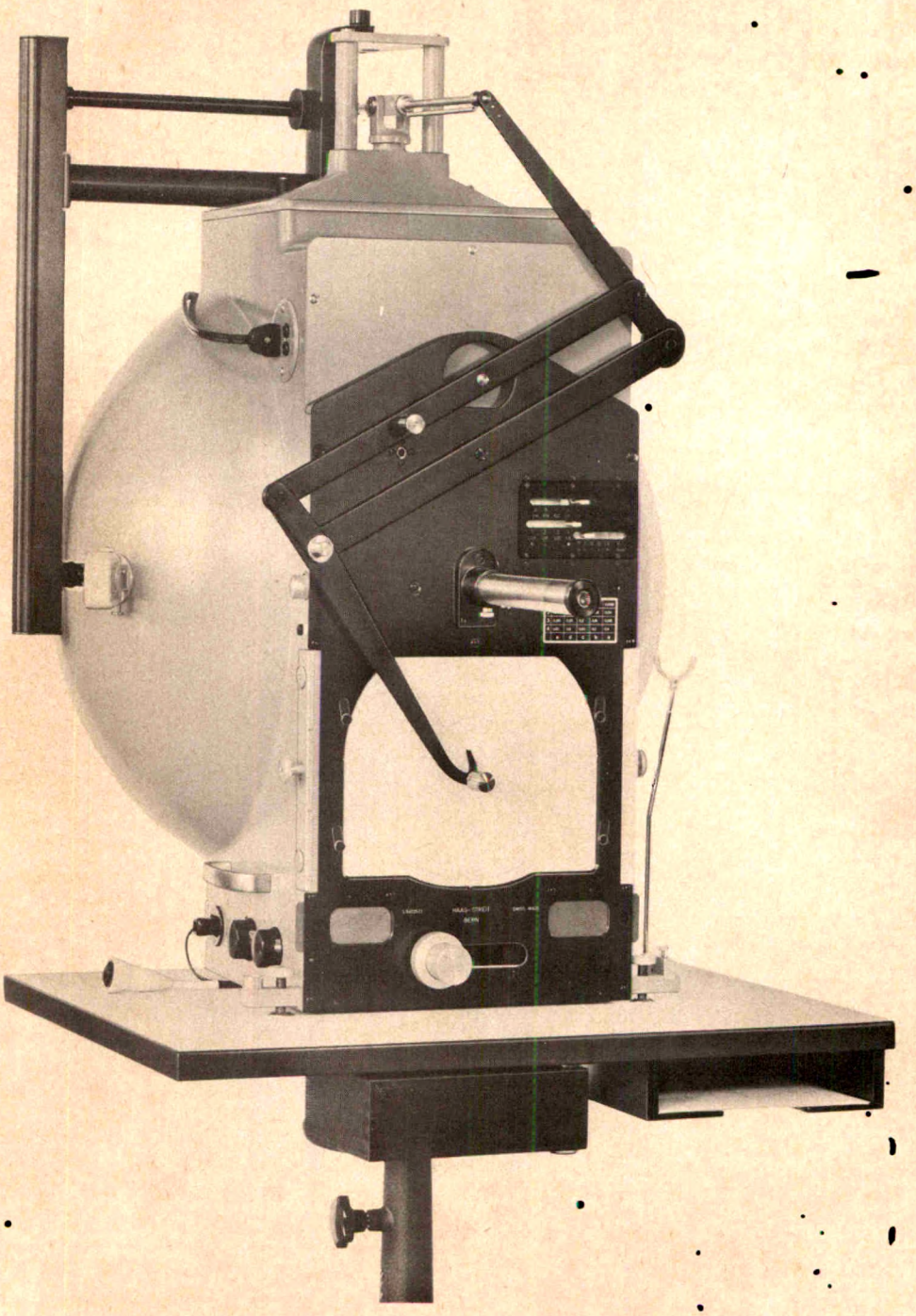


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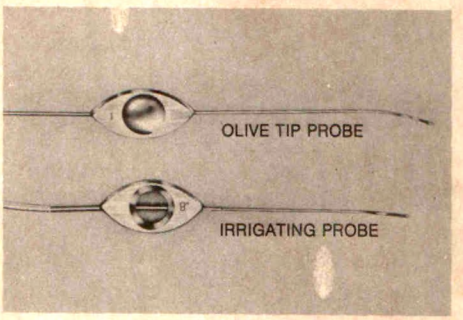
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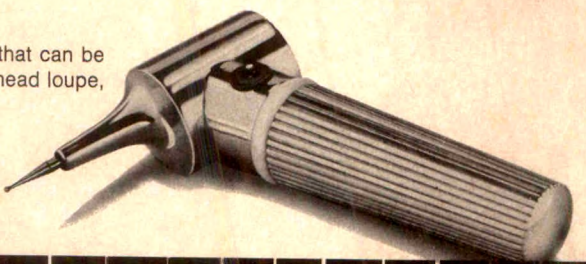


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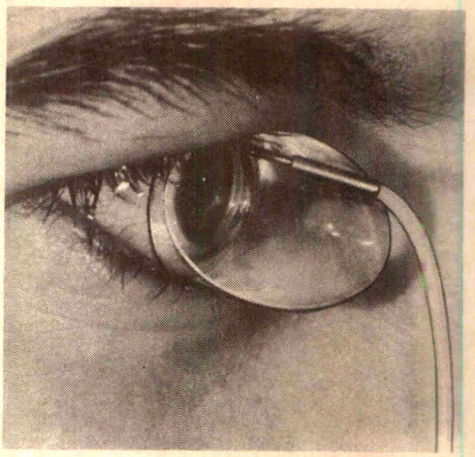
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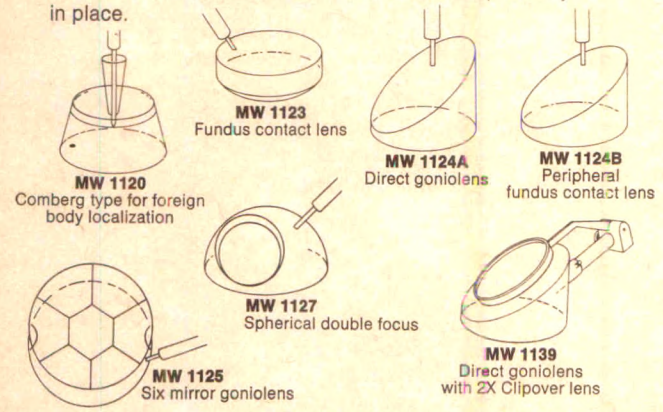
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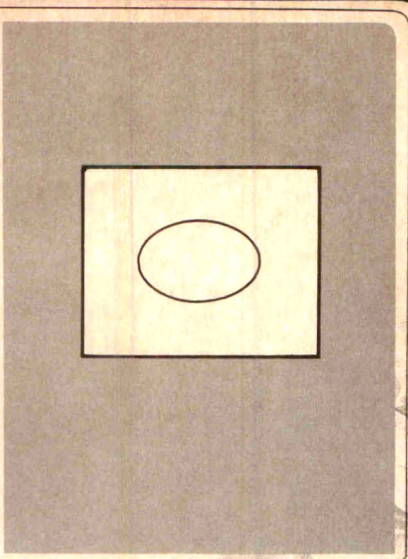
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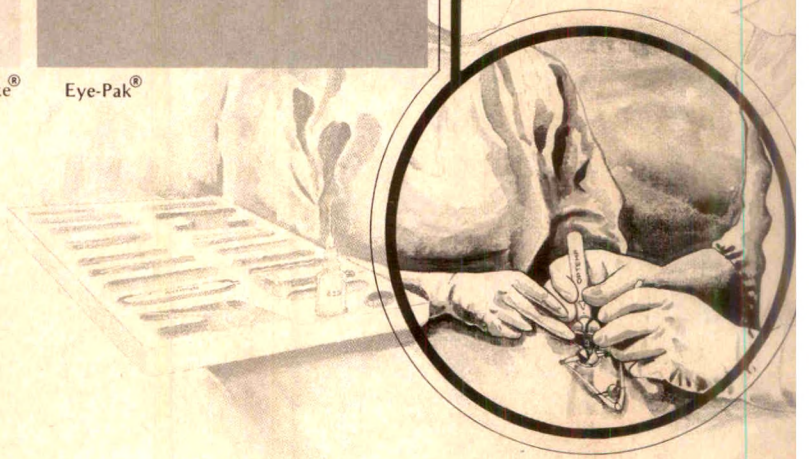
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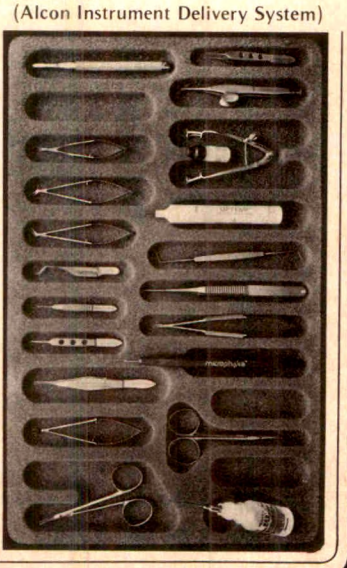
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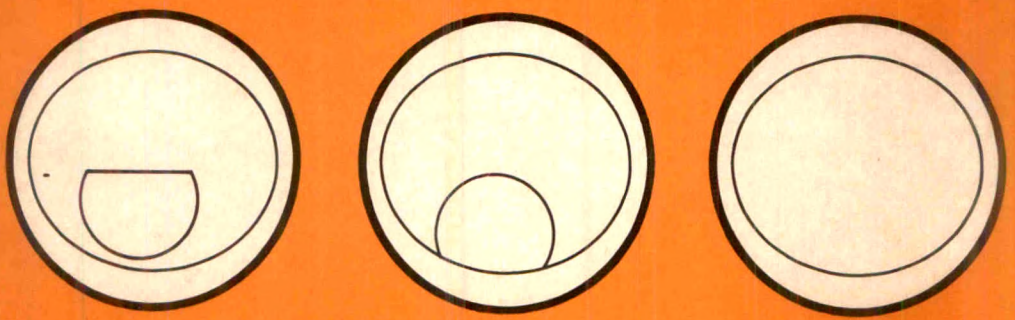
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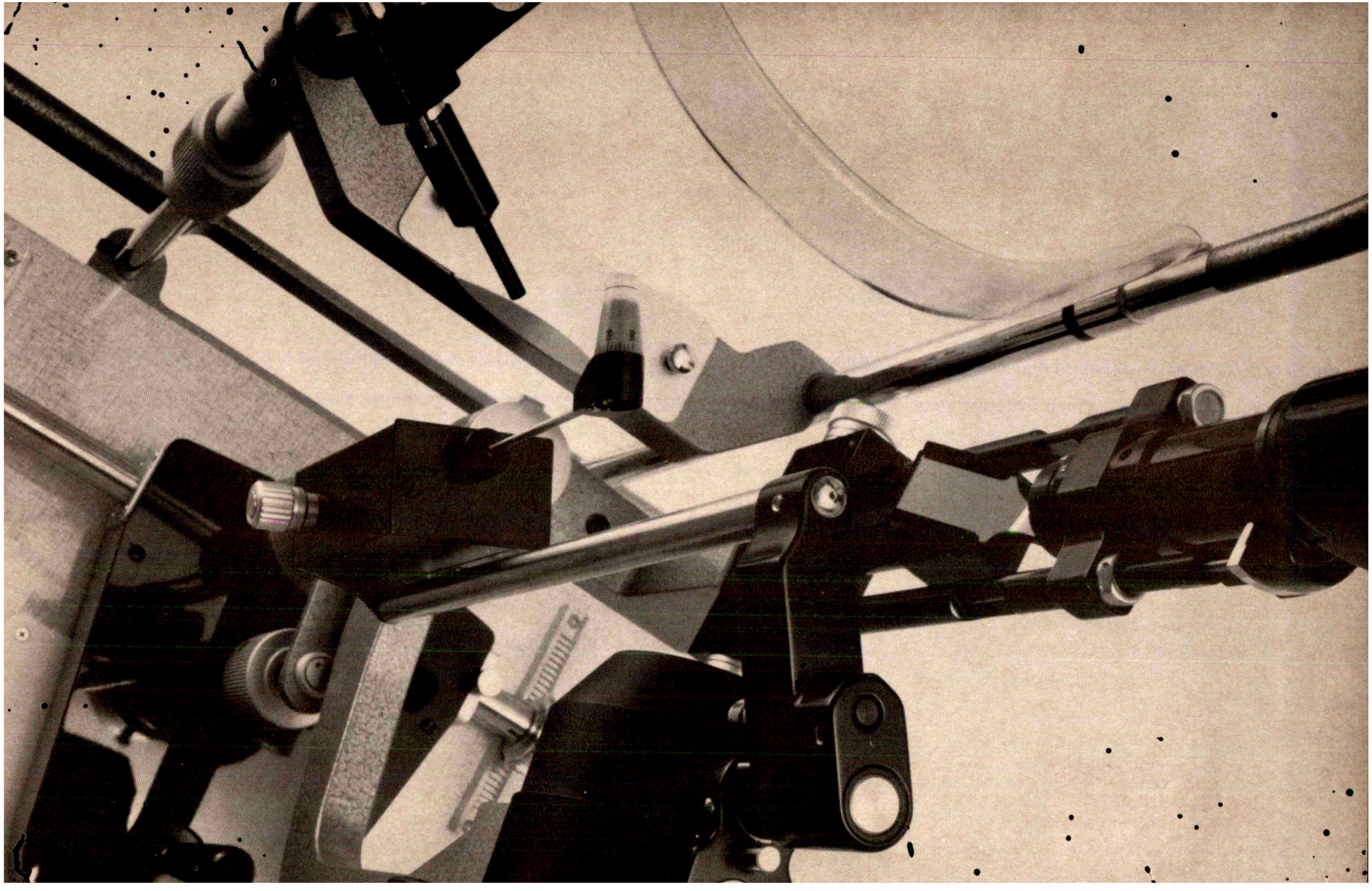
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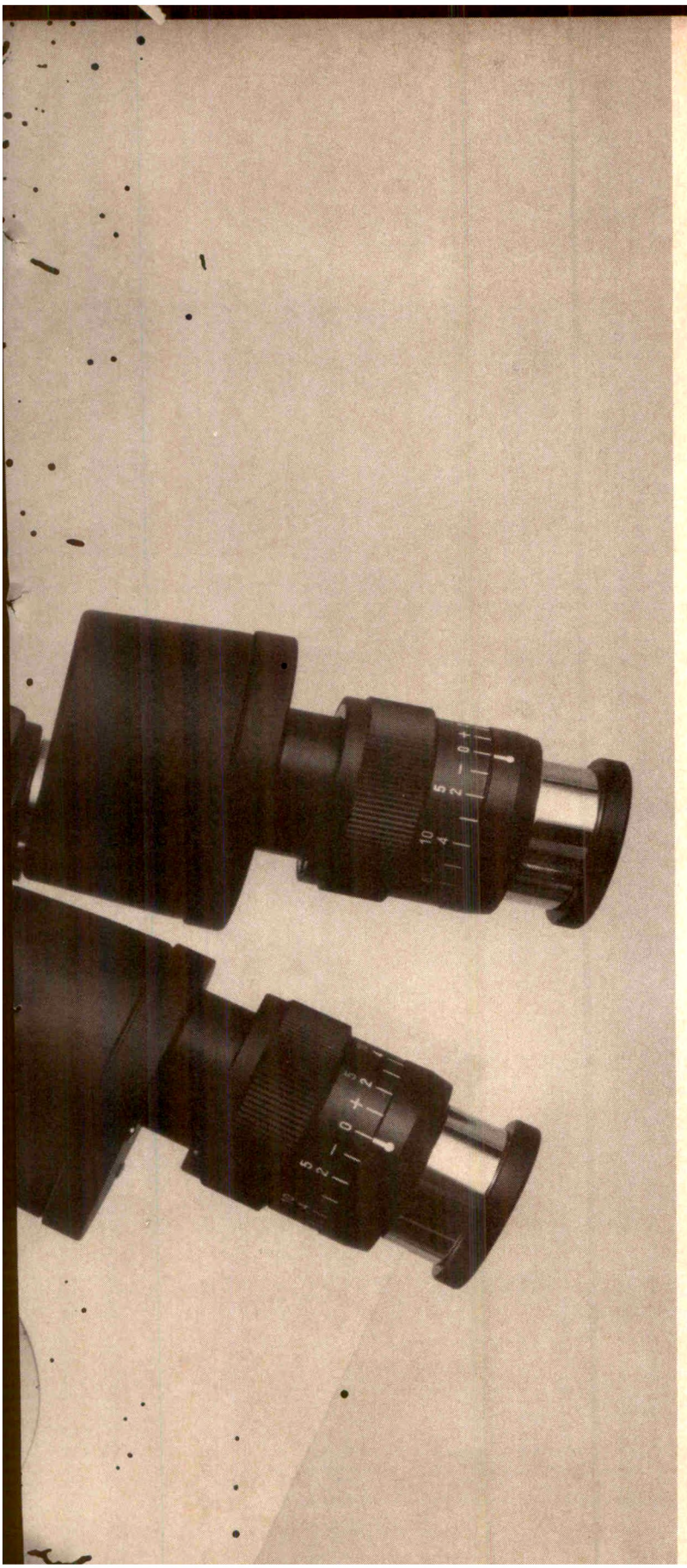
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INTRAOCULAR LENS MEETING
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(Registration will start Thursday, January 29, 1976, 5-9 p.m.
Meeting will start Friday at 9:00 a.m. and will end Sunday at 1:00 p.m.)

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COURSES

Course No. 1
Elementary Hard and Soft Contact Lens Fittings
Course Director: G. Peter Halberg, M. D.
Instructors: To Be Announced

Course No. 2
Therapeutic Lenses and Scleral Shells
Course Director: Herbert L. Gould, M.D.
Instructors: John W. Espy, M.D., Marsha Guibor

Course No. 3
Conventional Corneal Lenses: Fitting Principles and Problem Management
Course Director: Perry Rosenthal, M.D.
Instructors: To Be Announced

Course No. 4
Soft Contact Lens Fitting with Custom Designed Lenses
Course Director: Paul R. Honan, M.D.
Instructor: Herschell H. Boyd, M.D.

Course No. 5
Bifocal and Unifocal Contact
Lenses for the Presbyope
Course Director: Abraham Schlossman, M.D.
Instructors: Charles E. Clevenger, M.D., George H. Jones, M.D., George B. Pugh, M.D., Carolyn Schlossman, Norman Schmid, Sr., Frank Weinstock

Course No. 6
Therapeutic Hydrophilic Soft Lenses
Course Director: James V. Aquavella, M.D.
Instructors: Joseph A. Baldone, M.D., S. Arthur Boruchoff, M.D., John W. Espy, M.D., Richard H. Keates, M.D., Anthony B. Nesburn, M.D.

Course No. 7
Technological Aspects of Hard and Soft Contact Lenses (Basic Course—Instrumentation, Basic Lens Design, Modification and Follow-up Visits)
Course Director: Joseph Soper
Instructors: Frank Sanning, Kenneth Swanson, Ralph Sutton

Course No. 8
Aphakia—Lens Choice and Management
Course Director: Robert J. Crossen, M.D.
Instructors: Thomas R. Mazzocco, M.D., Robert C. Welsh, M.D.

Course No. 9
Clinical Aspects of Fitting the HydroCurve™ Lens
Course Director: James S. Russell, M.D.
Instructor: Susan Savage

Course No. 10
Cosmetic Fitting with the Bausch & Lomb Soflens
Course Directors: Ellis Gruber, M.D. and Charles O. Titus, M.D.
Instructors: To Be Announced

Course No. 11
Present Status of Silicone Lenses
Course Director: Chester J. Black, M.D.
Instructors: To Be Announced

Course No. 12
Hard and Soft Lenses in the Treatment of Ocular Pathology
Course Director: Frank B. Hoefle, M.D.
Instructors: Jorge N. Buxton, M.D., James Koverman

Course No. 13
Hard Contact Lenses
Course Director: Herschell H. Boyd, M.D.
Instructor: Paul R. Honan, M.D.

Course No. 14
Basics of Hydrophilic Lens Fitting—A Canadian Approach
Course Director: John F. Morgan, M.D.
Instructors: Ronald E. Groshaw, M.D., Bernard J. Slatt, M.D., Harold A. Stein, M.D., John D. Valberg, M.D.

Course No. 15
Orthokeratology
Course Director: Donald A. Fonda, M.D.
Instructors: Richard S. Fixott, M.D.

Course No. 16
The Use of Therapeutic Soft Contact Lenses
Course Director: Robert G. Webster, Jr., M.D.
Instructors: Walter J. Stark, M.D., H. Lee Stewart, M.D.

Course No. 17
Intraocular Lens Surgery, Indications and Contra-indications, Surgical Techniques
Course Directors: Jack Hartstein, M.D. and Richard P. Kratz, M.D.
Instructor: Herbert L. Gould, M.D.

Course No. 18
Surgical Aspects of Contact Lens Patients
Course Director: Pierre Guibor, M.D.
Instructors: Robert A. D'Amico, M.D., Marsha Guibor, Richard C. Troutman, M.D.

Course No. 19
Basic Fitting Technique and Workshop with the Warner-Lambert Softcon Lens
Course Director: Edward Shaw, M.D.
Instructors: To Be Announced

Course No. 20
Aphakic Correction
Course Director: Robert C. Welsh, M.D.
Instructors: Robert J. Crossen, M.D., Herbert L. Gould, M.D., Thomas R. Mazzocco, M.D., Charles Moore

INTRAOCULAR LENS COURSES, Sunday, February 1, 1976, 7-9 A.M.

Six intraocular lens courses will be given. The intraocular lens courses are so arranged that they will not conflict with the remainder of the courses.

Intraocular Lens Course Instructors are: James V. Aquavella, M.D., Stanley C. Becker, M.D., Jorge N. Buxton, M.D., Herve M. Byron, M.D., Robert C. Drews, M.D., Jack Hartstein, M.D., Francis C. Hertzog, Jr., M.D., Kenneth J. Hoffer, M.D., Herbert E. Kaufman, M.D., Richard H. Keates, M.D., Richard P. Kratz, M.D., David M. Worthen, M.D.

British Journal of Ophthalmology

June 1975 Vol. 59 No. 6

Editorial: A sympathetic approach to open-angle glaucoma

Ocular hypotensive effect of atenolol (Tenormin, I.C.I.) A new beta-adrenergic blocker. *M. J. Elliot, P. M. Cullen, and C. I. Phillips*

Effect of pindolol on intraocular pressure. *L. Bonomi and P. Steindler*

Effect of Adrenaline and Guanethidine in reducing intraocular pressure in rabbit's eyes. *D. E. P. Jones, D. A. Norton, J. Harvey, and D. J. G. Davies*

Quantitative lacrimal scintillography. I. Method and physiological application. II. Lacrimal pathology. *J. J. Hurwitz, M. N. Maisey, and R. A. N. Welham*

Radiography in functional lacrimal testing. *J. J. Hurwitz and R. A. N. Welham*

Cortical blindness in cranial arteritis. *I. H. Chisholm*

Homonymous hemianopia in multiple sclerosis. With report of bilateral case. *K. Hawkins and M. M. Behrens*

Lens fringe in homocystinuria. *M. S. Ramsey and D. H. Dickson*

Cataract aspiration-irrigation. Modified needle-tubing-handle combination for push-pull machine. *S. K. Bhargava and R. Gupta*

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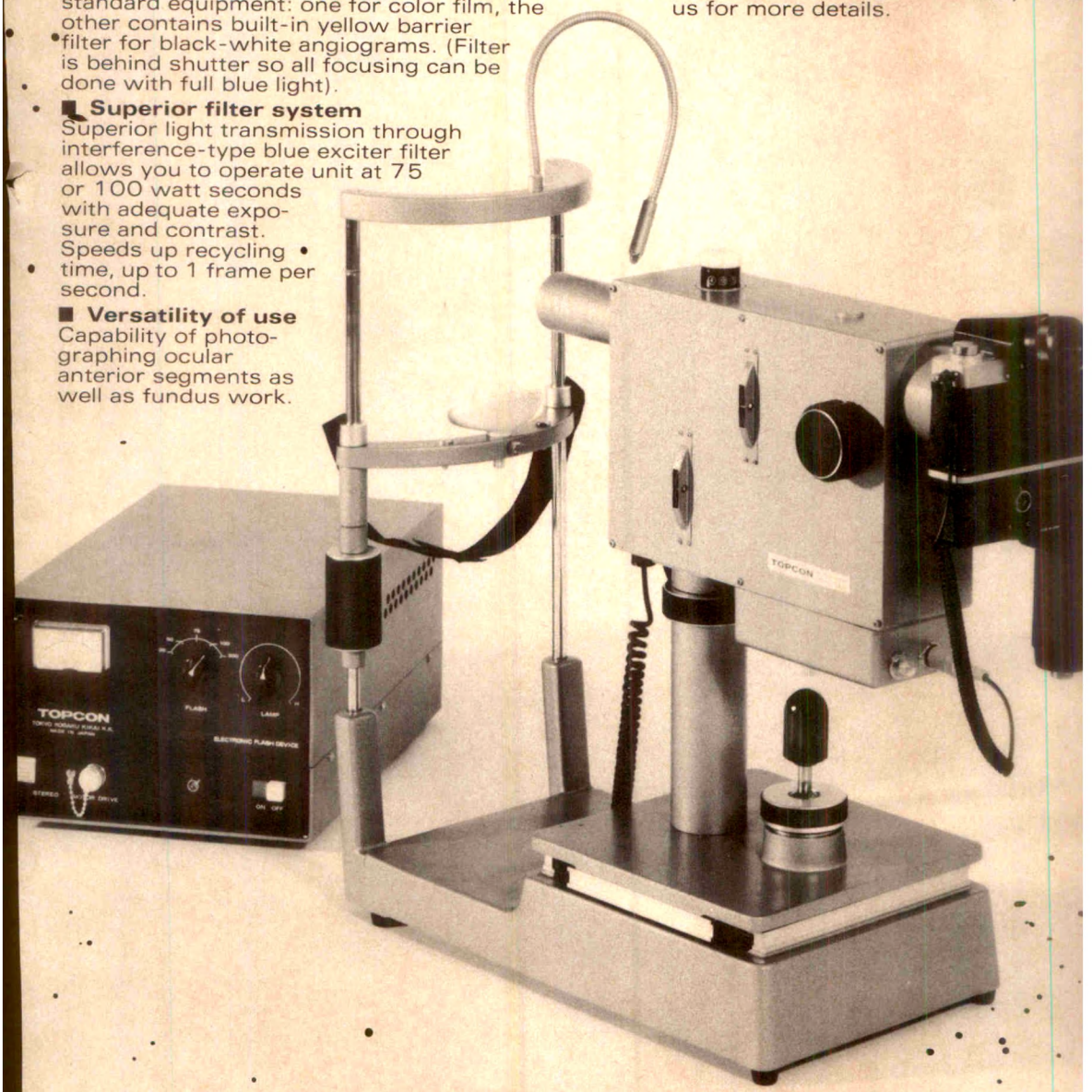
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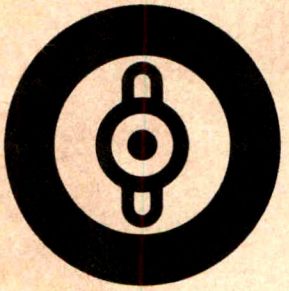
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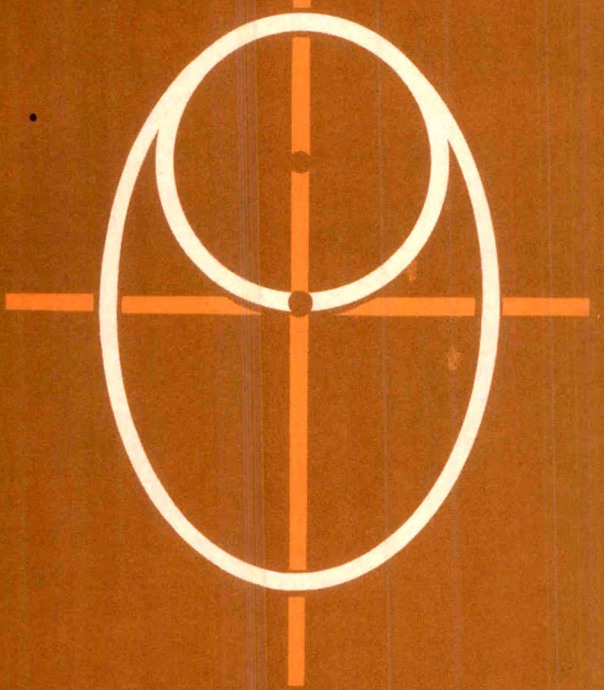
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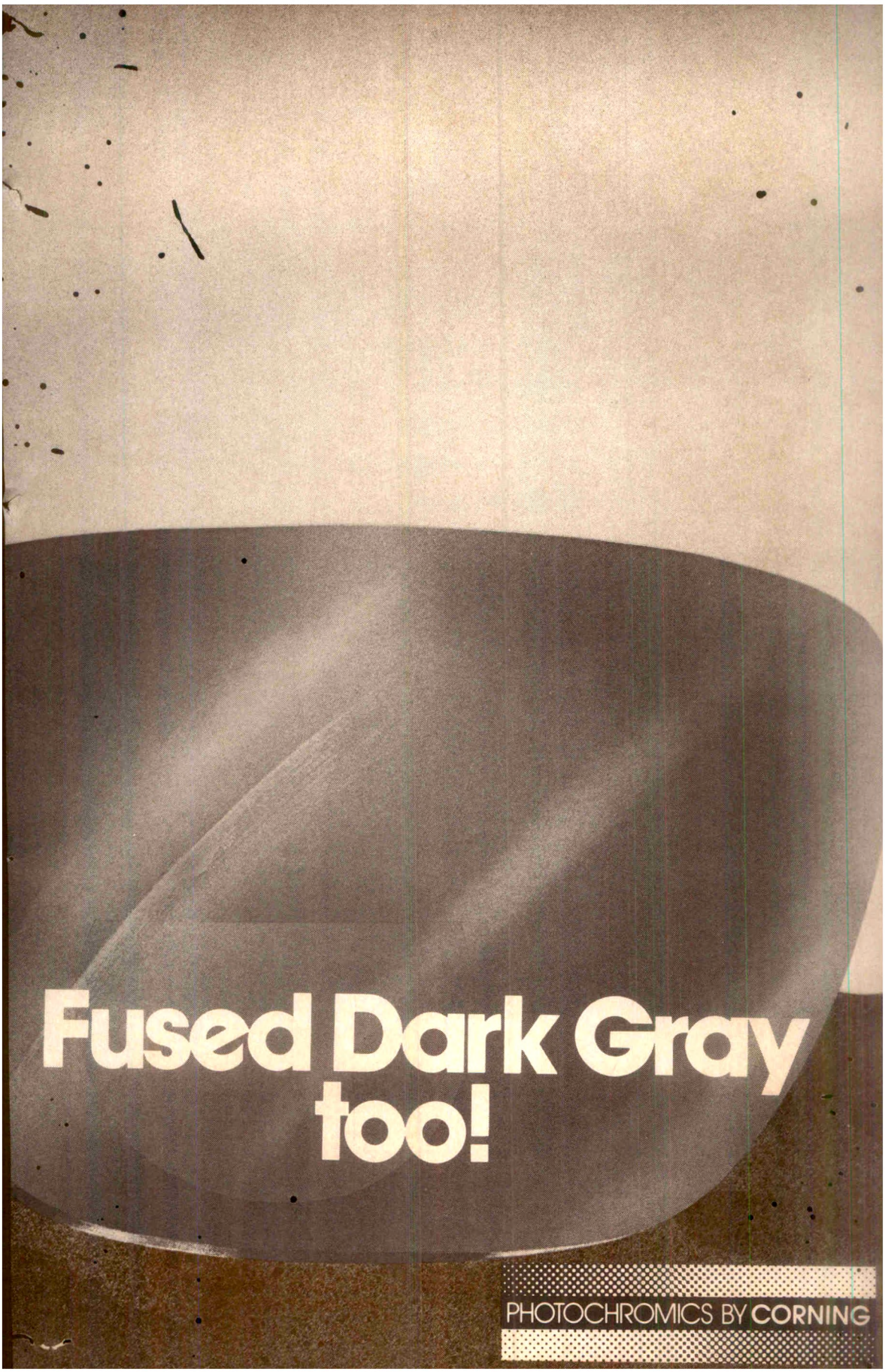
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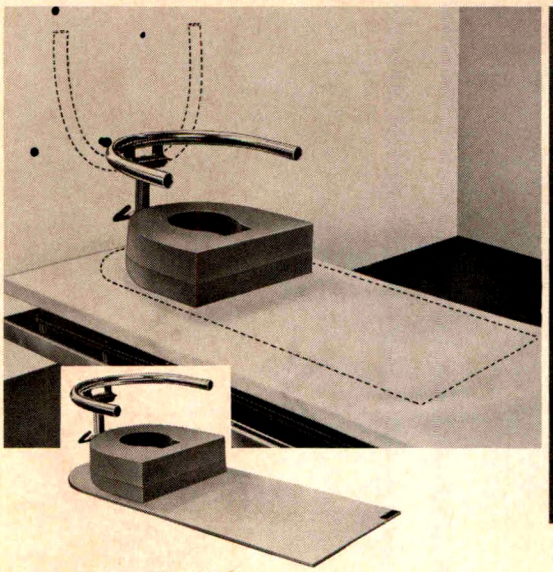
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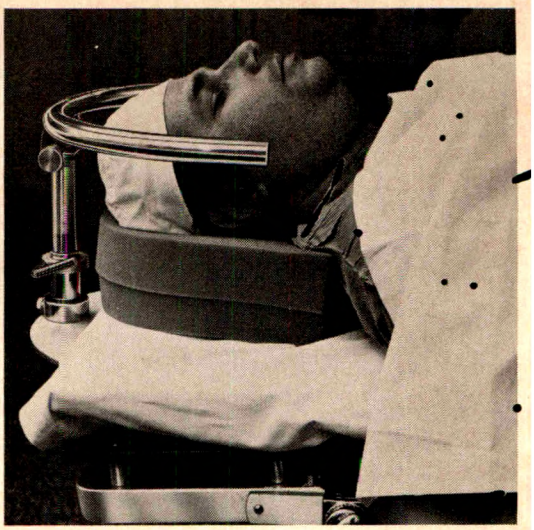
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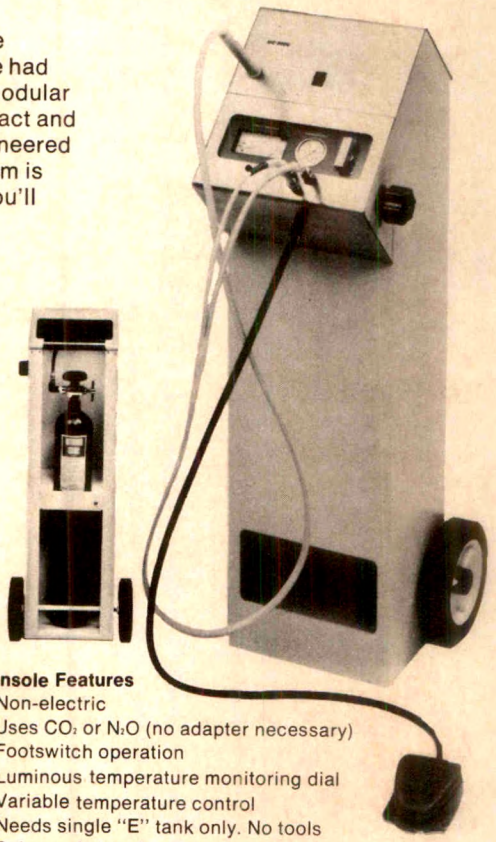
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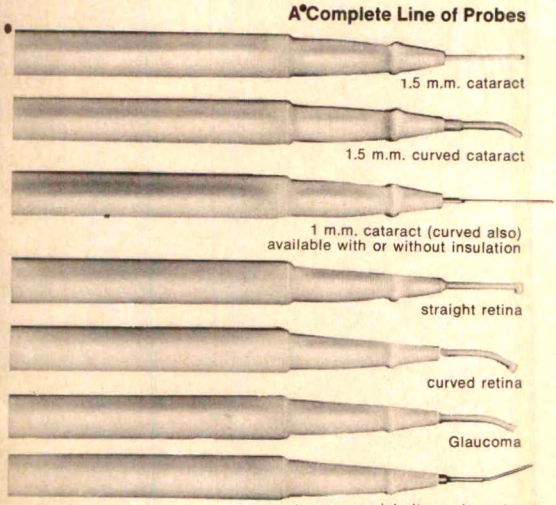
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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 80 DECEMBER, 1975 NUMBER 6

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THE THIRD PAN AMERICAN ASSOCIATION OF OPHTHALMOLOGY
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LORENZ E. ZIMMERMAN, M.D., AND RAMON L. FONT, M.D.
Washington, D.C.

Granulocytic sarcoma is a variant of granulocytic (myeloid) leukemia characterized by the formation of clinically apparent invasive and destructive neoplasms composed of immature cells of the granulocytic (myeloid) series.[1] Because of their classical greenish appearance produced by a pigmented enzyme called myeloperoxidase, these tumors have long been called chloromas, a name that was widely used long before it became generally recognized that they represent a localized manifestation of granulocytic leukemia.[2,3,*4] The name "chloroma" continues to be used,[5-10] but the currently preferred terms "granulocytic sarcoma" and "myeloid sarcoma" are more appropriate, as they reflect the cytologic composition of these tumors. While granulocytic sarcoma has recently gained considerable popularity as the name for this tumor, especially in the United States, it appears that the World Health Organization has settled on myeloid sarcoma as the preferred term for its classification. Of course, many other names have been used, and some are still in use: chloroleukemia, myelosarcoma, chloromyeloma, chloromyelosarcoma, myeloblastoma, tumorous myeloblastosis, granulocytic leukosarcoma, and the like.

Granulocytic sarcomas develop preferentially in bones or periosteum, especially those of the skull, and proptosis attributable to orbital involvement has long been recognized as a classical clinical feature.[1-3] Children are affected more often than adults, and boys more frequently than girls.[2-4,7] There are reasons for believing that these tumors have been encountered less frequently in the United States during recent years and that there may be considerable geographic variation in the incidence of granulocytic sarcomas, both as a form of leukemia and as a cause of proptosis.[8-11] Granulocytic sarcomas may appear at any time in the course of granulocytic leukemia.[1-7,11-13] When the tumor becomes clinically apparent before the leukemia has been recognized, the clinician is faced with a serious problem in differential diagnosis. Usually a biopsy is required, and the diagnostic problem is thus transferred to the pathologist. Even for the experienced surgical pathologist, the diagnosis may be

From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology, Washington, D.C. This study was supported in part by training grant EY-00032 from the National Eye Institute. Presented at the Tenth Pan American Congress of Ophthalmology, San Juan, Puerto Rico, April 23, 1975.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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*Forkner's monograph[2] contains an excellent early historical review of the literature on chloromas and a fine discussion of the various ophthalmologic manifestations of the leukemias. Edgerton's paper[3] provides a comprehensive review of the literature up to 1946.

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very difficult. This is especially true in those cases in which myeloblasts dominate the histologic picture and evidence of granulocytic differentiation is either not present or is overlooked. Use of histochemical staining for esterase activity has greatly improved our ability to make a definitive histopathologic diagnosis in such cases.[14-16]

Accurate, early histopathologic diagnosis is important for therapeutic and prognostic reasons. Even when the patient seems to be in good general health and has no recognized abnormalities in the peripheral blood, the clinician must be alert for the imminent appearance of other clinical and hematologic manifestations of acute granulocytic leukemia. Repeated examinations of the bone marrow as well as the peripheral blood are indicated, and one must also consider the possibility of going ahead with appropriate therapy for acute granulocytic leukemia even before overt systemic manifestations of the disease appear. The prognosis for untreated cases is poor.

The purpose of this report is to review our experience with 33 cases in which we have observed granulocytic sarcomas with orbital, palpebral, or ocular involvement.

Material and Methods

We reviewed all available slides and records from cases of proved or suspected orbital or ocular involvement in granulocytic (myeloid) leukemia on file in the Registry of Ophthalmic Pathology of the Armed Forces Institute of Pathology. In each of the 33 cases accepted for the study that formed the basis of this report, a tumor was evident clinically as well as pathologically. Each case also satisfied at least two of the following criteria: (1) The histopathologic picture was considered diagnostic, not only by us but also by consultants experienced in hematologic pathology, because of the convincing evidence of granulocytic differentiation; (2) stains for esterase activity* revealed positive reactions in the cytoplasm of the undifferentiated or poorly differentiated neoplastic cells; (3) there was hematologic evidence of granulocytic leukemia (Table 1). In 15 cases both hematologic confirmation and positive staining for esterase activity were available in support of the diagnosis; in ten cases there were supporting hematologic data but no positive staining for esterase activity; while in eight cases there was positive esterase activity but no hematologic confirmation. Most of the tumors in which we could not demonstrate esterase activity either were not properly fixed (formalin fixation is required) or we had neither blocks nor tissue available for examination. Most of the cases in which we had no hematologic confirmation were either very old cases in the Registry or they had been contributed from Asia, Latin America, or Africa, and the information could not be obtained. Efforts to obtain current follow-up information have been made in all cases except when the patient was known to have died, and in only three of the 33 cases do we have neither information about the ultimate outcome nor hematologic support of our diagnosis of granulocytic sarcoma.

A number of the cases have previously been presented elsewhere.[17-31] We believe this is the largest series of granulocytic sarcomas that has been gathered together for definitive clinicopathologic investigation.

* Leder's modification[15] of the method described by Moloney and co-workers[14] was used.

Results

Clinical data—The 33 patients ranged in age from 1 to 61 years, but three fourths of them were in their first decade (Tables 1 and 2), and their median age was 7 years. Males predominated over females, 19:13. Table 3, summarizing the geographical origin and racial data of these cases, indicates that 20 of the 33 patients were not white Americans. A disproportionate number of cases were from Asia, the South Pacific, and Africa.

In all but four cases, orbital or eyelid involvement (Figs. 1-5) was responsible for the initial clinical manifestation, and a biopsy

TABLE 1

CLINICAL AND FOLLOW-UP INFORMATION ON 33 CASES OF GRANULOCYTIC SARCOMA

Case No.	Age, yr,/ Race or Nationality/ Sex*	Ophthalmologic Features	Leukemia Evident	Esterase Activity Demonstrated	Course
1	5/?/F	Proptosis, L.E.; mass in left antrum and nasopharynx	No	Yes	Died 2 mos after exenteration
2	6/B/M	Proptosis; mass along nasal roof of orbit	Yes	No	Died 3 mos after excision of orbital tumor
3[24]	24/W/F	Rapidly growing tumor of eyelid 4 yrs after onset of leukemia	Yes†	No	Died 3 mos after excision of eyelid lesion
4[17]	6/W/F	Proptosis, R.E.; orbital tumor; rarefied lesions in x-ray films of skull	Yes	Yes	Died 2 yrs after onset
5[31]	1/B/F	Bilateral proptosis	Yes	Yes	Paraplegia; died 2 mos after biopsy
6	7/?/M	Proptosis	Yes	No	Died 19 mos after onset
7	3/B/F	Recurring proptosis	Yes	No	Died 2 yrs after onset; 1 yr after exenteration
8	7/P/F	Downward displacement of eye by tumor in upper outer orbit	No	Yes	Orbital involvement became bilateral; tumors in scalp and mandible
9[26,30]	7½/W/M	Lump in lower eyelid attached to orbital rim	Yes	Yes	Died 26 mos after biopsy
10	12/W/M	Proptosis	Yes	Yes	No information
11	1/W/F	Proptosis; bone destruction, maxilla	Yes	No	Died 2 mos after onset
12[29]	25/P/M	Proptosis; tumor filling orbit	No	Yes	Lost to follow-up after 9 mos
13	6/L/F	Orbital tumor	Yes	Yes	No information
14	1½/W/M	Appearance of acute dacrocystitis and cellulitis	Yes	No	Died 3½ mos after onset
15	5/V/M	Progressive proptosis	?	Yes	No information
16	4/W/F	Rapidly growing tumor, upper eyelid	?	Yes	No information
17[18,23]	9/W/M	Proptosis, blepharoptosis of eyelid; orbital mass	Yes	No	Died 2½ yrs after biopsy
18	10/W/F	Proptosis and blurred vision; bilateral papilledema	No	Yes	Splenomegaly; elevated uric acid; in remission 3+ yrs
19	7/V/M	Orbital tumor inferiorly displacing eye upward and inward	Yes	Yes	Proptosis became bilateral; splenomegaly; lost to follow-up
20[21]	10/W/F	Proptosis and mass at orbital rim	Yes	Yes	In remission over 2 yrs but blind from vitreous hemorrhage
21[22]	10/B/M	Proptosis; upper orbital mass displacing eye downward	Yes	Yes	Recurrence; enlarged nodes and liver; lost to follow-up
22	10/P/M	Orbital tumor	Yes	Yes	Died 18 mos after diagnosis of orbital tumor
23[19]	5½/I/M	Bilateral proptosis	Yes	Yes	Died 2 mos after onset
24[20]	14/W/M	Proptosis; retinal striae	Yes	No	Died 5 mos after onset
25	5½/W/F	Proptosis; mass in lacrimal gland	Yes	Yes	Died 18 mos after onset
26	20/W/M	Mass in lacrimal gland appeared while in remission, 6 mos after onset of leukemia	Yes†	Yes	Died 5 mos after biopsy
27	6½/W/M	Orbital tumor superiorly	Yes	Yes	Positive bone marrow 7 mos after biopsy; then lost to follow-up
28[27]	14/L/M	Proptosis	Yes	No	No information

(Continued on next page)

* A = African; B = black American; I = Indonesian; K = Korean; L = Latin American; P = Pakistani; V = Vietnamese; W = white; M = male; F = female.

† Cases in which leukemia was diagnosed before the granulocytic sarcoma appeared.

TABLE 1—(*Continued*)

Case No.	Age, yr, Race or Nationality Sex*	Ophthalmologic Features	Leukemia Evident	Esterase Activity Demonstrated	Course
29	3/A/M	Proptosis, R.E.; bilateral retinal striae; two masses in orbit	?	Yes	Paraplegia after exenteration; died
30	60/W/F	Orbital tumor	No	Yes	Hepatosplenomegaly
31[25]	5/W	Terminal proptosis and brain tumors	Yes†	Yes	Died 13 mos after treatment of leukemia
32[28]	6/W/M	Bilateral proptosis; uveitis and hypopyon while in remission after therapy	Yes†	Yes	Died 3 mos after onset of ophthalmic signs
33	8/W/M	Proptosis	Yes	Yes	Asymptomatic 4 mos after biopsy

was required for diagnosis or the tumor was resected before a hematologic diagnosis was made. In four cases the orbital or eyelid involvement (Figs. 6 and 7) developed late in the course of an established granulocytic leukemia. In most cases in which orbital or eyelid involvement was recognized before the leukemia, hematologic evidence in support of the diagnosis (Figs. 8 and 9) was obtained within two months (Tables 4 and 5), but in eight cases periods ranging from four to 15 months were required before leukemia could be diagnosed by examination of films of the peripheral blood or bone marrow.

TABLE 2

AGE DISTRIBUTION IN 33 CASES OF GRANULOCYTIC SARCOMA OF THE ORBIT*

Age, yrs	No. of Cases
0–5	11
6–10	14
11–20	4
21–30	2
Over 30	2

* Range, 1 to 61 yrs; median, 7 yrs.

TABLE 3

RACE OR NATIONALITY IN 33 CASES OF GRANULOCYTIC SARCOMA OF THE ORBIT

Race or Nationality	No. of Cases
American, white	13*
American, black	4
Latin American	2
European	3
African	1
Australian	1
Indonesian	1
Vietnamese	2
Korean	1
Pakistani	3
Unknown	2

* Includes cases from Canada.

The clinical picture at onset varied considerably. In some cases a discrete orbital tumor produced proptosis (Figs. 1 and 9) in a patient who seemed to be in good general health otherwise. In several such cases the tumor seemed to involve the lacrimal gland selectively rather than the orbital bones. Other patients presented with evidence of more diffuse involvement (Figs. 2-4), including the paranasal sinuses, other bones of the skull, or intracranial masses. In some cases the initial picture simulated that of an inflammatory process, or the history suggested a posttraumatic lesion. One 3-year-old girl (Fig. 1), who had had a biopsy that did not lead to a definitive diagnosis, was treated with corticosteroids for a presumed inflammatory pseudotumor and had a dramatic remission that lasted over a year. The proptosis recurred, did not respond to corticosteroid therapy, and another biopsy specimen was obtained, this time producing an initial diagnosis of rhabdomyosarcoma. Our review led to a diagnosis of granulocytic sarcoma, but since hematologic evidence of

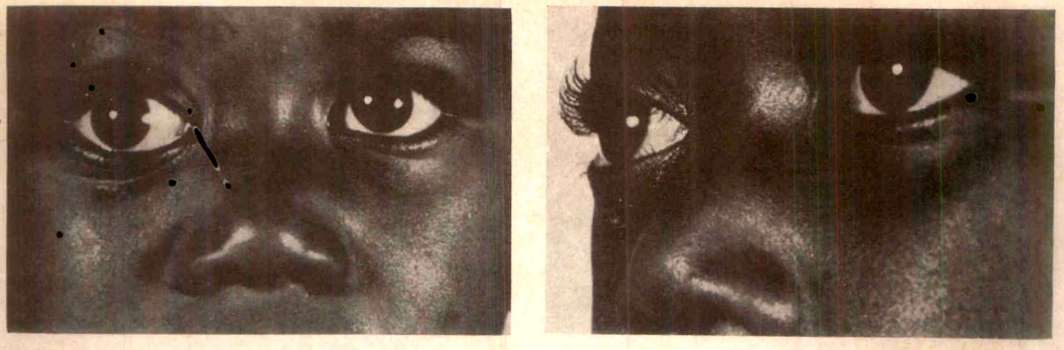


Fig. 1 (Zimmerman and Font). Case 7. Slight proptosis and downward displacement of right eye by an orbital mass located superiorly in a 3-year-old girl in good general health. Radiologic and hematologic findings were negative. Neurofibromatosis was suspected preoperatively (AFIP Negs. 73-4006-1 and 2).

leukemia was not obtained, exenteration and radiation (4,500 rads) were used. The leukemic picture began to emerge just as radiation therapy was completed, 3½ months after exenteration; within a year the child had died. The 9-year-old boy shown in Figure 9, left, is another who was thought to have rhabdomyosarcoma after biopsy and was scheduled for exenteration. Routine blood counts on admission had been nonrevealing,



Fig. 3 (Zimmerman and Font). Case 14. This 1½-year-old boy with extensive involvement of the lower eyelid and orbit of only one week's duration was suspected of having an acute dacryocystitis. Initial hematologic and radiologic studies were nonrevealing and the child appeared to be in good general health (AFIP Neg. 67-2679).



Fig. 2 (Zimmerman and Font). Case 24.[20] This 14-year-old boy, who had a history of having sustained a minor injury to the left forehead three months before this picture was taken, developed proptosis of the left eye and diplopia. Radiologic studies revealed a diffuse destructive process involving the left orbit, frontal bone, greater sphenoidal wing, and temporal bone. Venography showed evidence that the tumor extended into the cranium as well as the orbit. Preoperative hematologic studies revealed no abnormalities, but on the fifth postoperative day, when the patient developed nosebleeds and hemoglobinuria, the peripheral blood count rose to 119,000 with 70% blast cells (AFIP Neg. 75-5671).



Fig. 4 (Zimmerman and Font). Case 5.[21] Extreme bilateral proptosis from bilateral orbital involvement in a 15-month-old girl whose initial hematologic and radiologic studies had been nonrevealing. The child had had repeated infections of the upper respiratory tract, and Letterer-Siwe disease was suspected (AFIP Neg. 55-10355).

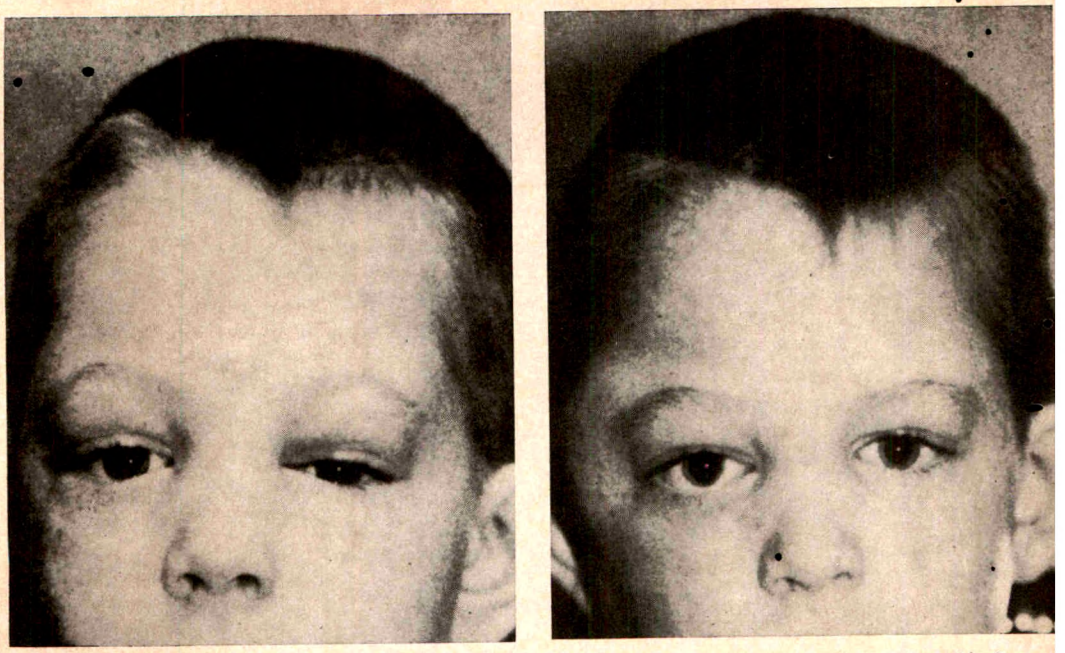


Fig. 5 (Zimmerman and Font). Case 9.[26,30] Left, Six months before this picture was taken this 8-year old boy had a rapidly enlarging lump in the left lower eyelid. Laboratory investigations yielded negative results, and the initial diagnoses considered after the tumor was excised were reticulum cell sarcoma and Hodgkin's disease. Subsequently the child noted diplopia, and examination revealed proptosis, visual acuity reduced to 20/50, and papilledema, L.E. Only after a subtemporal decompression to control markedly increased cerebrospinal fluid pressure had been performed did hematologic studies begin to reveal evidence in support of the diagnosis of granulocytic sarcoma (AFIP Neg. 73-3271-2). Right, This picture, taken when the diagnosis of acute myeloid leukemia was established, ten months later, reveals extensive involvement of the right temporal region (AFIP Neg. 73-3271-3).

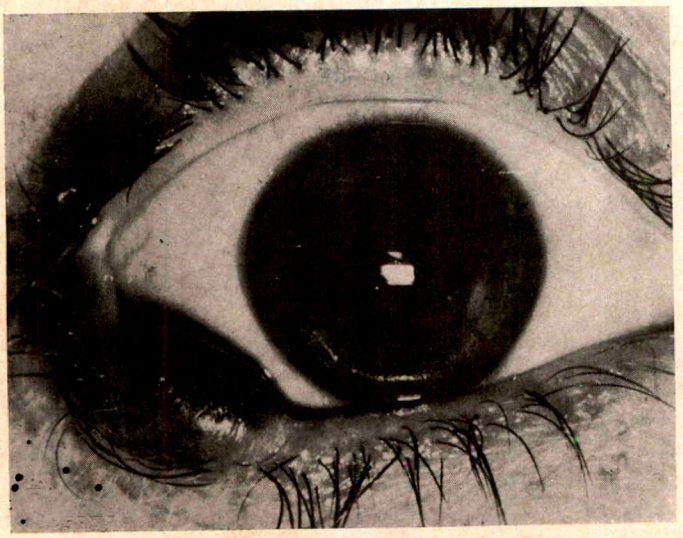


Fig. 6 (Zimmerman and Font) Case 3.[24] This rapidly growing tumor developed in the eyelid of a 24-year-old woman who had been treated for myeloblastic leukemia for four years. She died three months after the eyelid lesion was excised (AFIP Neg. 65-2993-2).



Fig. 7 (Zimmerman and Font). Case 26. This 20-year-old man, while in a temporary remission after treatment for acute myeloid leukemia, developed a mass in the lacrimal gland. He died six months later (AFIP Neg. 73-17196).

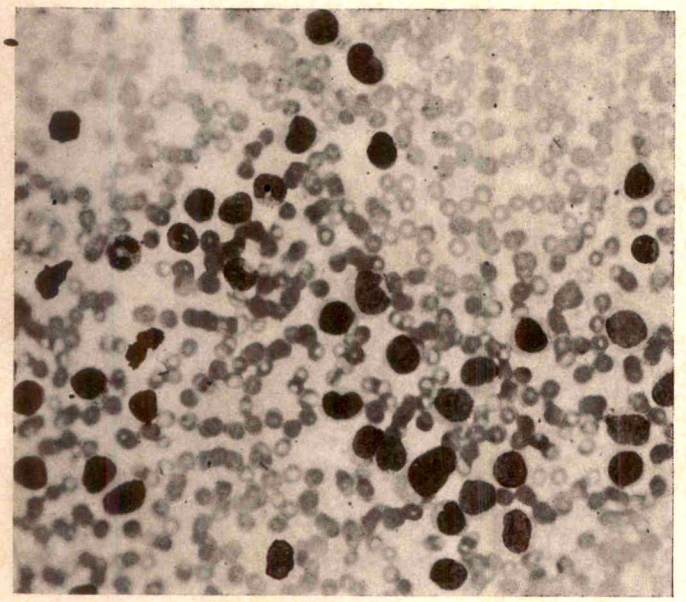


Fig. 8 (Zimmerman and Font). Case 14. Immature cells of the myeloid series, which appeared in the peripheral blood of the patient shown in Figure 3, about 2½ months after biopsy. At this time, when the hematologic diagnosis of acute blastic leukemia was made, radiologic study revealed a lesion in the radius, where the patient had noted a lump in the wrist (×350; AFIP Neg. 68-2091).



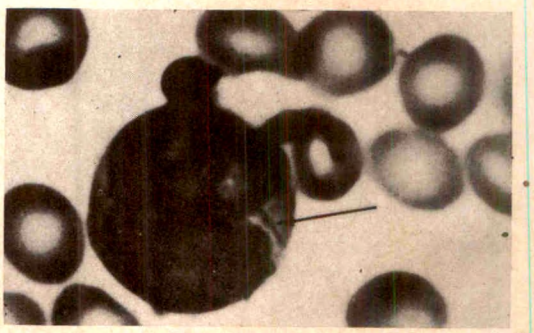


Fig. 9 (Zimmerman and Font). Case 17. Left, This 9-year-old boy in good general health had had a drooping left upper eyelid for four months and proptosis in the left eye for one month. Biopsy led to a tentative diagnosis of rhabdomyosarcoma, and an exenteration of the orbital contents was scheduled. Upon review of the sections, the probability of granulocytic sarcoma was suggested and hematologic data were solicited. Reevaluation of the peripheral blood revealed 25% blast cells. Right, Auer rods (arrow) were observed in blast cells, which accounted for 44% of cells in the bone-marrow aspirate (AFIP Negs. 75-5883-1 and 75-5883-2). (From Karp.[23])

TABLE 4

INTERVAL BETWEEN ONSET OF ORBITAL MANIFESTATIONS AND HEMATOLOGIC EVIDENCE OF LEUKEMIA IN 20 CASES OF GRANULOCYTIC SARCOMA

Interval, mos	No. of Cases
0–2	12
4–6	4
7–8	2
Over 1 yr	2

TABLE 5

INTERVAL BETWEEN BIOPSY OF ORBITAL TUMOR AND HEMATOLOGIC EVIDENCE OF LEUKEMIA IN 20 CASES OF GRANULOCYTIC SARCOMA

Interval, mos	No. of Cases
0–2	14
3–4	3
6–9	3

but after we suggested the diagnosis of granulocytic sarcoma and asked for hematologic reevaluation, evidence of acute myeloblastic leukemia was obtained (Fig. 9, right). Another child, a 1½-year-old boy, thought to have an acute dacryocystitis (Fig. 3) was admitted to the hospital for antibiotic therapy, but after a week of penicillin and chloromycetin therapy failed to control progression of the disease, a biopsy was performed. Clinical laboratory and radiologic investigations had been nonrevealing. The biopsy then lend to a tentative diagnosis of reticulum cell sarcoma or Hodgkin's disease, and x-ray therapy produced an almost complete disappearance of the lesion. Two months later a lump in the wrist was discovered, and radiologic study showed evidence of a "metastasis" to the radius. By that time hematologic evidence of an acute myeloblastic leukemia had become obvious (Fig. 8).

In several cases both orbits (Figs. 4 and 5) were involved, either from the beginning or soon after onset.

A noteworthy greenish appearance of the tumor was rarely described clinically or at the time of surgery, but in some cases it was obvious in fresh surgical specimens or at autopsy. In this series it did not seem to be a helpful diagnostic sign.

In 19 cases the patient is known to have died, usually within two or three months after onset and in 17 of these cases there was hematologic evidence of leukemia (Table 6). The longest survival among these fatal cases was 30 months. One living patient (Case 18), who was treated for her granulocytic sarcoma even though a hematologic diagnosis of leukemia was not established, has survived over three years. She has had an enlarged spleen, hyperuricemia, and hyperglobulinemia.

Histopathologic observations—These granulocytic sarcomas were most frequently composed of masses of relatively uniform undifferentiated cells with scanty to moderately abundant cytoplasm and round to reniform nuclei (Figs. 10 and 11). Searching generally revealed cells showing evidence of granulocytic differentiation (Fig. 12), and in a few cases the presence of numerous eosinophilic myelocytes and metamyelocytes interspersed among the more primitive cells made the diagnosis relatively easy for us. Giemsa stains were sometimes useful in the demonstration of granulocytic differentiation (Fig. 12, left). A survey of the diagnoses entertained by the contributing pathologists

TABLE 6

FOLLOW-UP DATA IN 33 CASES OF GRANULOCYTIC SARCOMA OF THE ORBIT

Status	Total Cases	No. of Cases with Leukemia
Died (in 2 to 30 mos*)	19	17
Lost to follow-up	9	5
In remission (2 to 3 yrs*)	2	1
Currently under treatment	3	2
Total	33	25

* These time intervals are with respect to the onset of ophthalmologic manifestations.

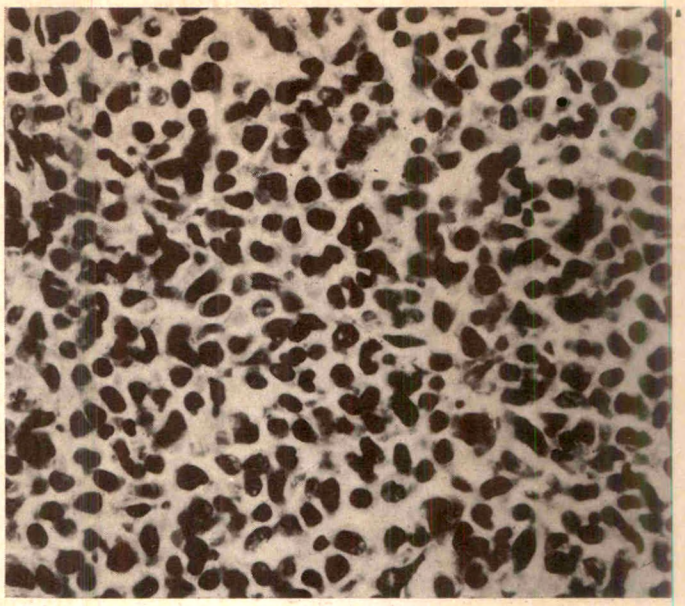


Fig. 10 (Zimmerman and Font). Case 14. This field from the biopsy of the lower eyelid and orbital tumor of the patient shown in Figure 3 reveals an infiltrate of poorly differentiated cells with large nuclei that tend to be reniform and scanty eosinophilic cytoplasm. A definitive diagnosis of granulocytic sarcoma was not made in this case until the hematologic picture (Fig. 8) emerged (hematoxylin and eosin, ×525; AFIP Neg. 68-2095).

(Table 7) shows that these cases do constitute difficult diagnostic problems. In only three of the 18 cases used for Table 7 did the local pathologist consider the tumor to be granulocytic sarcoma or a manifestation of leukemia.

The frequency with which other diagnoses such as malignant lymphoma, neuroblastoma, and rhabdomyosarcoma were suggested reflects the rather primitive cytologic composition of these tumors. In two cases the number of eosinophilic granulocytes that were present led to the suspension of eosinophilic granuloma.

The stain for esterase activity (Fig. 13) proved especially useful in reevaluating old

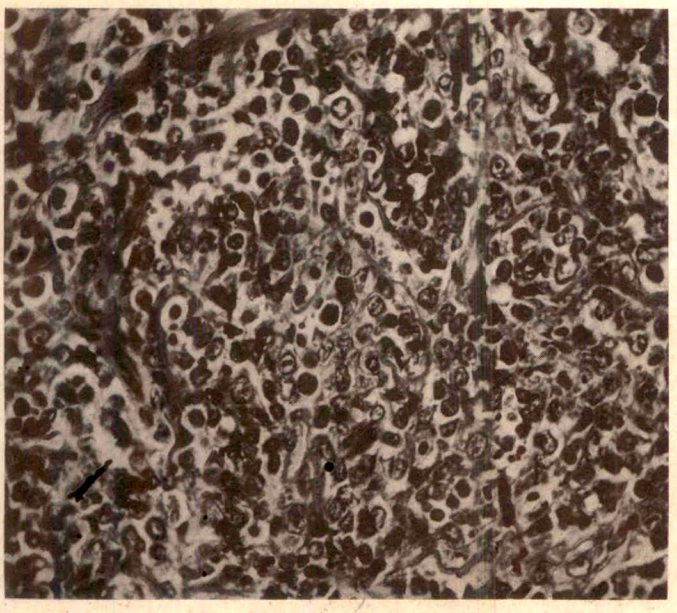


Fig. 11 (Zimmerman and Font). Case 7. This recurrent orbital tumor from the patient shown in Figure 1 is composed mainly of undifferentiated cells that some pathologists believed to be rhabdomyoblastic, but others considered to be reticulum cells. The polymorphic character of the tumor and the evidence of granulocytic differentiation noted by some reviewers led them to suspect granulocytic sarcoma several months before the hematologic picture settled the controversy (hematoxylin and eosin, ×380; AFIP Neg. 64-2158).

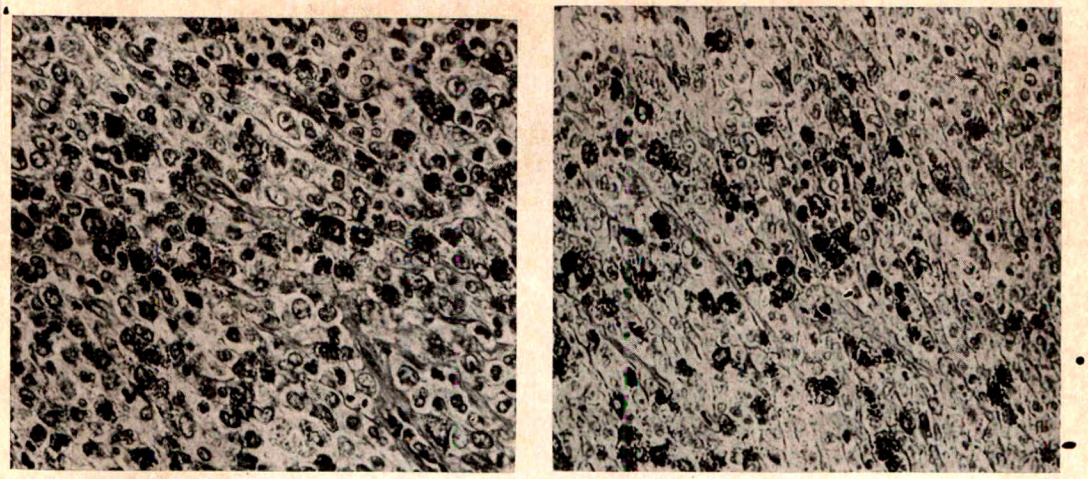


Fig. 12 (Zimmerman and Font). Case 30. Left, While the majority of cells in the field are completely undifferentiated, many other immature cells contain dark-red cytoplasmic granules characteristic of eosinophilic myelocytes and metamyelocytes (hematoxylin and eosin, ×380; AFIP Neg. 74-12831). Right, An adjacent section, stained with Giemsa, reveals the cells with bright eosinophilic granules more conspicuously (×410; AFIP Neg. 74-12830).

TABLE 7

DIAGNOSES SUGGESTED BY ORIGINAL PATHOLOGISTS IN 18 CASES OF GRANULOCYTIC SARCOMA OF THE ORBIT*

Original Diagnosis	No. of Cases	
Malignant lymphoma		11
Reticulum cell sarcoma	7	
Histiocytic lymphoma	1	
Hodgkin's disease	1	
Type not specified	2	
Leukemia		3
Myelogenous	1	
Granulocytic sarcoma	2	
Rhabdomyosarcoma		5
Neuroblastoma		3
Miscellaneous malignant tumors		4
Sarcoma	1	
Ewing's tumor	1	
Angiosarcoma	1	
Carcinoma	1	
Nonmalignant conditions		6
Eosinophilic granuloma	2	
Hand-Schüller-Christian disease	1	
Inflammatory pseudotumor	3	

* Not included here are four cases in which leukemia had been recognized before the granulocytic sarcoma, five cases in which the initial pathologic studies were made at AFIP, and six cases in which the original pathologic diagnosis was not made known to us. In several cases more than one diagnosis had been suggested.

cases in which hematologic data were either not available or had been controversial. Our experience with Cases 1 and 5 provides good examples. Case 1, the oldest in this series, was received in consultation at the old Army Medical Museum in 1926. The contributing pathologist had made a diagnosis of "small cell sarcoma," while the original diagnosis made by the staff at the Army Medical Museum was "carcinoma." Only many years later in the course of a comprehensive review of all orbital tumors on file at the AFIP did we recognize this tumor as a probable granulocytic sarcoma. A leukemic blood picture had never been detected during the life of this patient. The positive stain for esterase activity confirmed our tentative diagnosis. In Case 5 (Fig. 4) the original clinical and histopathologic diagnosis had been Letterer-Siwe disease. Subsequently, after the acute "blastic" leukemia became apparent, and even after a complete autopsy had been done, none of the hematologists or pathologists who studied the case at the local hospital or at the AFIP considered the leukemia to be definitely of the acute myeloid

type. The case was reevaluated in the course of our current study, and the stains for esterase activity made on sections cut from blocks of tissue obtained at autopsy and stored in paraffin for 19 years were strikingly positive (Fig. 14). Valid results, however, depend on the availability of wet tissue or paraffin-embedded material that has been well fixed in formalin. One must be able to identify the cells with positively stained (red) cytoplasm as being the primitive or immature blastlike cells. Some common sense must be used in evaluating results of staining for esterase activity, and in some cases better cytologic detail must be required than in others. For example, if the problem is one of determining whether a mass of undifferentiated cells is composed of neuroblasts, rhabdomyoblasts, or lymphoblasts on the one hand or myeloblasts on the other, any significant degree of esterase activity will be helpful in ruling out neuroblastoma, rhabdomyosarcoma, and lymphosarcoma; but if the problem involves the determination of whether a lesion is inflammatory or a granulocytic sarcoma, then one must require better preservation of cytologic details in evaluating stains for esterase activity. Similarly, if a lesion has become ulcerated or secondarily inflamed and many leukocytes are present, then the evaluation of stains for esterase activity is more difficult, inasmuch as the neutrophils normally give a positive esterase reaction.

In two cases uveal infiltration was observed. In one of these, which involved a 3-year-old African boy (Case 29) who was not known to have had leukemia, clinical examination had revealed rapidly progressive unilateral proptosis, a palpable mass superonasally, and bilateral retinal edema. The affected eye was enucleated in the course of removal of the orbital tumors. Histopathologic study revealed leukemic infiltration of the choroid posteriorly (Fig. 15, top) as well as a granulocytic sarcoma surrounding the trochlea (Fig. 15, bottom). In the other case, involving a 6-year-old boy (Case 32), myeloid leukemia had been recognized and treated, and a remission obtained. While receiving maintenance therapy the child complained of blurred vision, photophobia, and epiphora. Examination revealed mild exophthalmos (bilateral), a left hypopyon, bilateral uveitis, and infiltration of both irides. The left disk was blurred by a vitreous hemorrhage and visual acuity reduced to finger counting. Bone-marrow studies at this time did not reveal any abnormalities. Nodular lesions developed in the conjunctivae of both

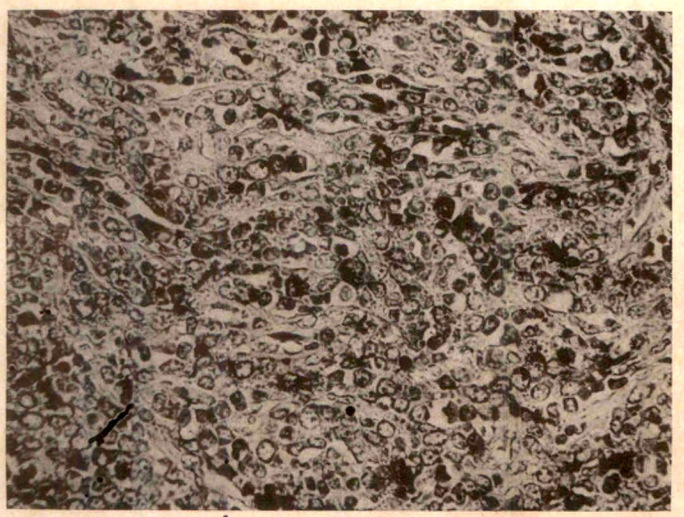


Fig. 13 (Zimmerman and Font). Case 21. The stain for esterase activity reveals many poorly differentiated cells with dark-red cytoplasmic granules indicative of granulocytic differentiation (Leder stain, ×300; AFIP Neg. 72-12553).

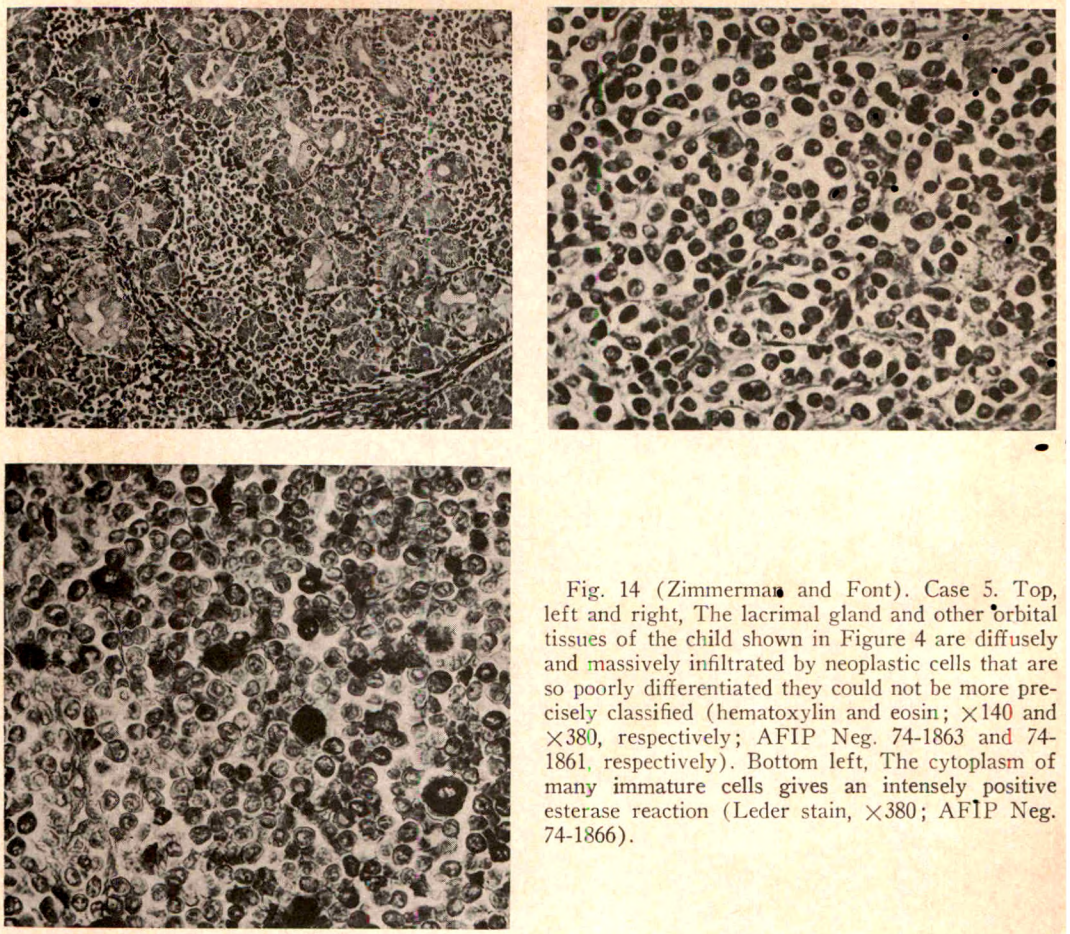


Fig. 14 (Zimmerman and Font). Case 5. Top, left and right, The lacrimal gland and other orbital tissues of the child shown in Figure 4 are diffusely and massively infiltrated by neoplastic cells that are so poorly differentiated they could not be more precisely classified (hematoxylin and eosin; ×140 and ×380, respectively; AFIP Neg. 74-1863 and 74-1861, respectively). Bottom left, The cytoplasm of many immature cells gives an intensely positive esterase reaction (Leder stain, ×380; AFIP Neg. 74-1866).

eyes. The bilateral proptosis increased, and the fundus of the right eye became obscured. The eyes obtained post mortem revealed large epibulbar nodules and diffuse thickening of the iris and ciliary body (Fig. 16) resulting from infiltrates of immature leukemic cells, many of which stained positively for esterase.

Discussion

The distributions of the cases in the present series by age and sex are characteristic in that granulocytic sarcomas occur mainly in children, boys being more frequently affected than girls.[2-4,7] Of special interest is the fact that only 13 of the 33 patients were white Americans or Canadians, an unusually skewed distribution for case material on file in the Registry of Ophthalmic Pathology. The fact that so few of these cases were contributed from the United States confirms the impressions of several American writers that these tumors have been encountered less frequently in recent years and that they may be more prevalent in certain other geographic regions. In Duke-Elder's review of the world literature between 1951 and 1971, all of the reported cases with orbital involvement were found in the foreign literature. All of Forkner's illustrations of orbital chloromas published in his book[3] were of Chinese children.

In Uganda, where the leukemias of childhood are observed much less frequently than in America or Europe, granulocytic sarcoma appears to develop with unusual regularity[8,9] and is disproportionately frequent whether compared with other forms of leukemia or other causes of proptosis in childhood.

Davies and Owor[8] observed only 32 cases of leukemia in African children, but 13 had myeloid leukemia. Eight of these children had chloromas, six of which involved the orbit. Templeton,[9] whose main interest was not leukemia but rather orbital tumors in African children, found that granulocytic sarcomas accounted for eight of 60 cases of proptosis, second only to Burkitt's tumor, which was the diagnosis in 28 cases. Rhabdomyosarcoma, the most frequent primary malignant tumor of the orbit in the United States and Europe, accounted for only one of the 60 cases in Templeton's series.[9] Thus, although the frequency of Burkitt's tumor in equatorial Africa is well known, it is noteworthy that as a cause of proptosis it was only 3½ times more frequent than granulocytic sarcoma.

These tumors are also observed with unusual frequency in Japan, where there has been a greatly increased incidence of granulocytic leukemia among survivors of atomic-bomb irradiation at Hiroshima and Nagasaki.[11] Granulocytic sarcomas were found at autopsy in 23 of 338 cases of granulocytic leukemia, but the incidence of this tumor as compared to that of leukemia was no greater among the exposed than among the nonexposed. It was concluded, therefore, that granulocytic sarcoma cannot be considered a

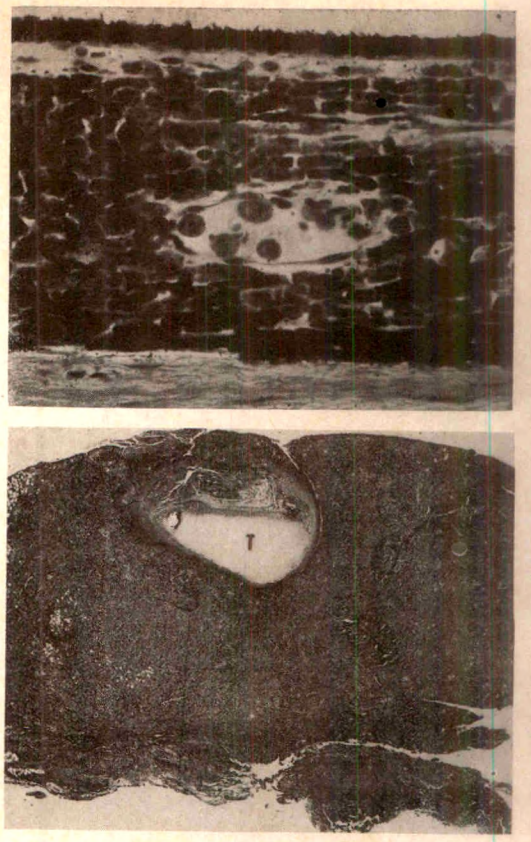


Fig. 15 (Zimmerman and Font). Case 29. Top, Large undifferentiated leukemic cells infiltrate the choroid and are also present in the lumen of a choroidal vessel (hematoxylin and eosin, ×380; AFIP Neg. 74-7328). Bottom, The granulocytic sarcoma surrounds the trochlea (T) (hematoxylin and eosin, ×10; AFIP Neg. 74-7325).

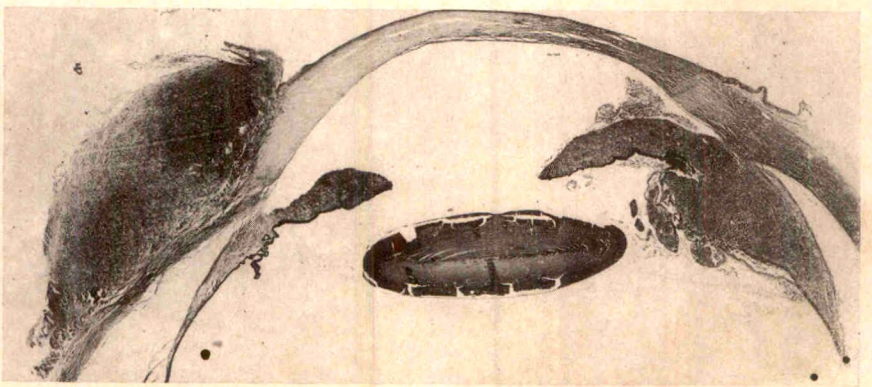


Fig. 16 (Zimmerman and Font). Case 32. Epibulbar granulocytic sarcoma and diffuse thickening of iris and ciliary body resulting from leukemic infiltration in a boy who developed bilateral proptosis while in therapeutic remission (hematoxylin and eosin, ×5; AFIP Neg. 74-11039).

"marker" for the development of radiation-induced leukemia.[11]

In striking contrast to these examples of the frequency of granulocytic sarcoma in Africa and Asia is the experience at the Mayo Clinic.[10,32] Burgert and co-workers[32] recently reviewed their data based on 758 cases of leukemia in children less than 15 years of age, of which 679 were acute lymphocytic leukemia. Among the 79 cases of nonlymphocytic leukemia, only 20 were considered to be of the acute granulocytic type, and none of the patients were described as having chloromas, though one child had previously received radiation therapy elsewhere for a tumor of the orbit. This experience confirms what Henderson stated[10]:

> . . . considering its prevalence at one time, the incidence of chloroma seems to have decreased markedly. The reason for this is open to speculation. Nevertheless, some modern clinicians have never observed a case, and no examples were found in the Mayo Clinic series.*

Orbital involvement typically occurs in patients whose leukemia has already been recognized or whose initial work-up reveals evidence of acute leukemia. Such typical cases are recognized and treated without a biopsy, or if biopsy is done to confirm the clinical impression, the pathologist is tipped off as to what to expect. When an apparently healthy child develops a rapidly growing tumor in the orbit or eyelid and the general medical and laboratory investigations are nonrevealing, the clinician naturally considers rhabdomyosarcoma and neuroblastoma and resorts to a biopsy to make the final diagnosis. It is that type of case that is most likely to find its way to the AFIP, because, as is evident from Table 7, the pathologist often has considerable difficulty in making a correct definitive diagnosis. The cases in the present series are undoubtedly weighted with diagnostic problems. Even in these cases, however, hematologic support for the diagnosis of granulocytic sarcoma can usually be obtained soon after the onset of ophthalmologic manifestations (Table 4). One should not rely entirely on routine examinations of the peripheral blood when the possibility of granulocytic sarcoma is under consideration. Buffy-coat preparations or bone-marrow examination, or both, may be diagnostic even in the absence of abnormalities in the peripheral blood, as reported by Templeton,[9] Mason, Demaree, and Margolis,[13] and the hematologists who studied several of the patients in the present series.

Although a long latent period between the appearance of the localized mass and the development of a leukemic blood picture is unusual, several cases have recently been reported in which the appearance of tumors preceded overt leukemia by intervals of three months to four years.[5,6,11–13,18,26] In eight of the 33 cases we have collected here, hematologic evidence of leukemia was not observed until after latent periods of four to 15 months after the onset of ophthalmologic manifestations.

We have little to contribute to a discussion of therapy, but at least two observations may be made. In presenting our clinical data, we have already mentioned Case 7, in which corticosteroid therapy, used because the proptosis was thought to be caused by an inflammatory pseudotumor, apparently had a therapeutic effect that lasted a year. Unfortunately, it also served to delay definitive diagnosis and institution of more effective therapy. Treatment of this disease has been notoriously unsuccessful and, at best, only temporarily effective. The one patient (Case 18) who has survived over three years (the longest thus far) is therefore of particular interest. In that case intensive treatment was begun without hematologic confirmation that the girl had leukemia. Although leukemia has never been documented in that case, few bone-marrow studies have been made (at the parents' request), and there have been some findings consistent with leukemia such as splenomegaly and hyperuricemia. The fact that this child's illness has had such a favor-

* Statement based on a consecutive series of 465 orbital tumors observed over a 19-year period and classified histopathologically.

able course suggests that other vigorous therapeutic efforts should be made as soon as a definitive histopathologic diagnosis is possible, rather than waiting for the leukemic blood picture to emerge.

A rapidly growing orbital tumor in a child should suggest rhabdomyosarcoma, granulocytic sarcoma, Burkitt's lymphoma, and metastatic neuroblastoma, provided that retinoblastoma can be excluded by ophthalmoscopic examination. Granulocytic sarcoma is likely to present a somewhat more polymorphic cell population, although in some of the most difficult cases myeloblasts dominate the scene to such a degree that evidence of granulocytic differentiation is not observed without the aid of stains for esterase activity. Regarding the frequency with which contributing pathologists have suspected malignant lymphomas, especially reticulum cell sarcoma, we should point out that with the exception of Burkitt's tumor, which may be encountered in the United States,[33,34] malignant lymphoma is a rare orbital tumor in children. In our experience it has been a good rule to suspect any orbital tumor that looks like a malignant lymphoma to be a granulocytic sarcoma and to undertake appropriate hematologic studies and to stain sections for esterase activity. In equatorial Africa, where both Burkitt's tumor and granulocytic sarcoma are so prevalent (the two together accounting for 60% of the 60 cases of proptosis in children reported by Templeton[9]), the problem in differential histopathologic diagnosis can be difficult. This is well covered by Berard and others.[16] When the degree of cellular polymorphism is marked, and especially when eosinophilic granulocytes are numerous, one may be misled into considering the lesion an inflammatory pseudotumor, eosinophilic granuloma, or Hodgkin's disease. Our experience shows, however, that if the tissue specimen is adequate and well fixed, the pathologist should have no great difficulty in recognizing the basically neoplastic character of the myeloblastic cells.

One of the recurring problems that makes diagnosis so difficult is the crush artifact, a problem we encounter frequently, especially with small biopsy specimens. All ophthalmic surgeons should realize how careful they must be and how gently they should treat tissues to be examined. This is particularly true in the case of the leukemia-lymphoma group, because hematopoietic tissues are the ones most easily damaged. No tissues require more care during the biopsy procedure and during fixation than these. Rough handling and squeezing of the tissues must be avoided by the surgeons, nurses, pathologists, and technicians. Buffered formalin should be used for fixation. Bouin's solution and Zenker's fixative are undesirable at best, and they are unsuitable if stains for esterase activity are to be prepared. Bony lesions requiring decalcification are also unsuitable for esterase staining. While a positive stain for esterase activity observed in the cytoplasm of a primitive cell is generally diagnostic of myeloid leukemia,* negative results are often meaningless, as they may be the consequence of having only technically unsuitable material available for study.

Summary

The clinicopathologic review of 33 well-documented cases of granulocytic sarcoma on file in the Registry of Ophthalmic Pathology confirmed the facts that this tumor is encountered mainly in children, that boys are affected more frequently than girls, and that white Americans appear to be less vulnerable than other ethnic groups. While granulocytic sarcoma is a variant of granulocytic leukemia, the tumor may appear before, after, or concomitantly with hematologic evidence of leukemia. In the present series only four of the 33 patients were already known to have leukemia when they were first seen by an ophthalmologist for their orbital, ocular,

* Mast cells also exhibit an esterase-positive cytoplasm, but neoplastic proliferations of mast cells are very rare, and we have never seen a mast cell tumor in the orbit or eyelids.

or adnexal lesions. The Leder stain has proved extremely helpful in arriving at a definitive histopathologic diagnosis. Accurate diagnosis is important to prevent inappropriate medical or surgical treatment and to indicate the need for vigorous antileukemic chemotherapy. Prognosis at best is poor.

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OCULAR FINDINGS IN NIEMANN-PICK DISEASE

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Niemann-Pick disease, an inherited disturbance with autosomal recessive transmission, is characterized by the widespread storage of lipids, chiefly sphingomyelin and cholesterol, in the reticuloendothelium and nervous system and in the viscera.[1]

Crocker[2] recognized four forms of the disease and, more recently, Neville and associates[3] described six phenotypes. Brady and associates[4] and Schneider and Kennedy[5] demonstrated a deficiency in the enzyme sphingomyelinase in types A and B.

The classic type A Niemann-Pick disease begins in early infancy with severe mental retardation, hepatosplenomegaly, and cachexia. Usually death occurs by the age of 2 or 3 years.[1] Ocular symptoms are inconstant. Several authors[1,6,7] reported the presence of macular cherry-red spots in one third to one half of the afflicted children. Robb and Kuwabara[8] mentioned lenticular opacities and a peculiar corneal clouding in some patients.

The ocular histopathology of type A Niemann-Pick disease includes ballooned, lipid-laden, retinal ganglion cells, vacuolated cells within the choroid, and lipid deposits within the glial cells of the optic nerve.[9–12] Robb and Kuwabara[8] reported the first electron microscopic study of the eyes of a patient with Niemann-Pick disease, in which they described more widespread involvement.

We describe the clinical observations, the histopathologic findings, and the ultrastructural appearance of the eyes in a case of type A Niemann-Pick disease with two distinct types of lipid inclusions.

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CASE REPORT

A 5-month-old girl, the third child of nonconsanguineous parents, had difficulty in feeding, as well as frequent episodes of vomiting, since birth. Her physical and psychomotor development was retarded. Her two siblings were not affected.

On physical examination, the patient appeared to be emaciated. There was a marked hepatosplenomegaly. Ophthalmoscopic examination showed bilateral pallor of the disks and macular cherry-red spots. Vacuolated lymphocytes were present in the peripheral blood. Bone marrow and liver biopsy specimens disclosed foam cells. Ultrastructural study of these biopsy specimens and a fibroblast culture confirmed the diagnosis of Niemann-Pick disease.

Laboratory studies showed an increase of sphingomyelin elimination in urine (1,960 nmoles/100 ml; normal, 80 to 320). Serum glycolipid count was elevated (glucosylceramide: 2,260 nmols/100 ml, normal 800 to 1,200; lactosylceramide: 1,000 nmols/100 ml, normal 400 to 650). Serum sphingomyelin and phosphatidylcholine counts were normal.

Follow-up examination showed poor psychomotor and physical development. From the age of 1 year, the child presented signs of cortical irritation, confirmed by electroencephalography, with convulsions and respiratory arrests. After repeated respiratory infections, the child died at 3½ years of age. Eight days before death, there was a brownish corneal clouding. The ophthalmoscopic signs persisted. A conjunctival biopsy was performed at this time.

METHODS

The eyes were obtained within a few hours after death. The left eye was prepared for light microscopy. It was fixed in 10% formaldehyde solution. The globe was cut in three portions: two calottes, one superior and one inferior, and a median horizontal portion, 5 mm thick. The median portion was again divided into two parts, one of which was embedded in paraffin and the other in gelatin. The chorioretinal tissues of the calottes were used for flat mounted preparations and for trypsin digest preparations. The right eye was prepared for electron microscopy. It was transected and placed in 4% glutaraldehyde (Millonig buffer, pH 7.4). Immediately, each ocular structure was dissected into 2-mm square

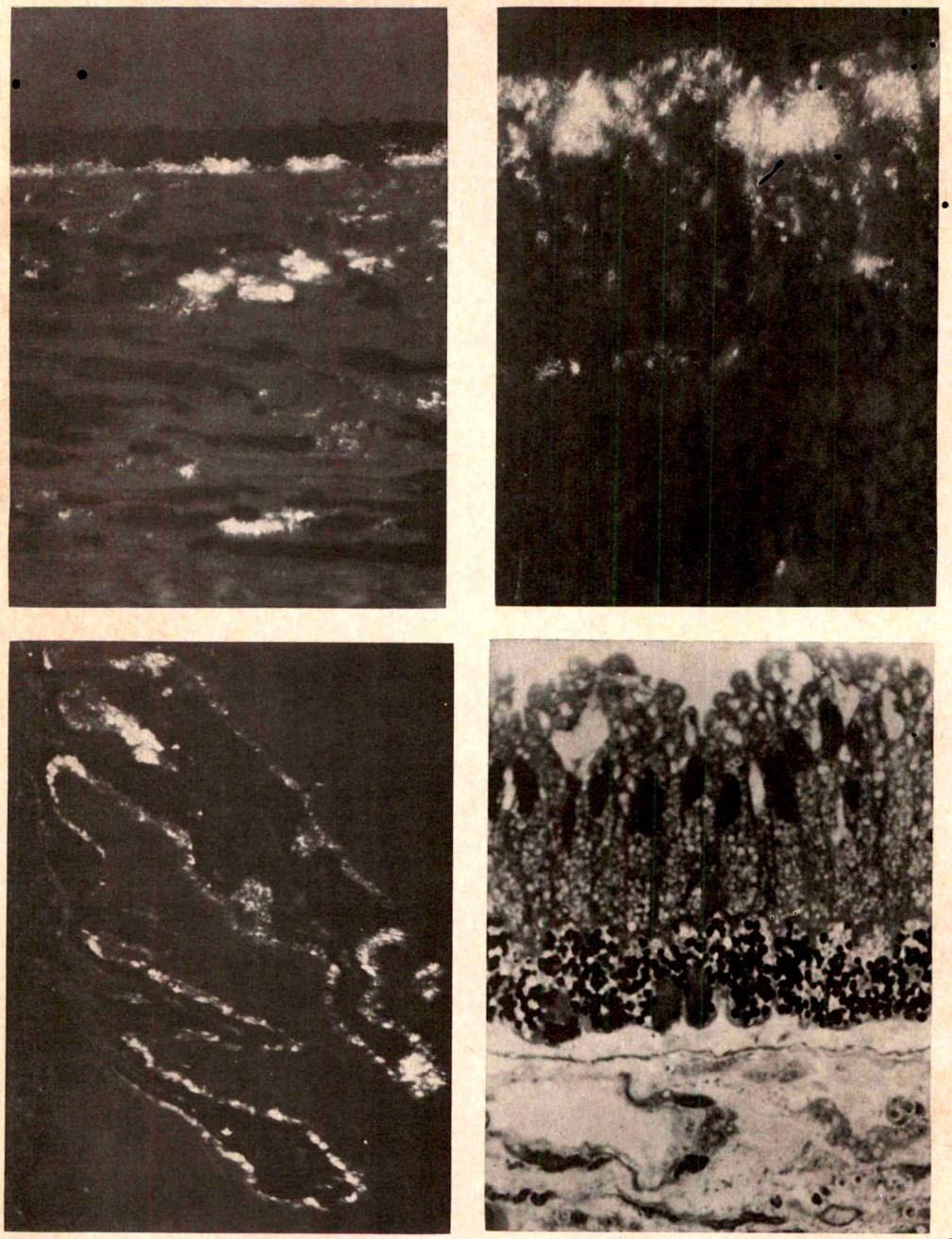


Fig. 1 (Libert, Toussaint, and Guiselings). Frozen sections photographed with crossed polarizing filters. Birefringent material is evident in the basal portion of the retinal pigment epithelium and in the fibrocytes of the choroid (top left, ×450), in the retinal ganglion cells, the amacrine cells, the Müller's cells (top right, ×450), and in the nonpigmented layer of the ciliary process (bottom left, ×50). Bottom right, Semi-thin section of the epithelial layers in the ciliary process. The nonpigmented epithelium shows a striking profusion of clear vacuoles. Some vacuoles are visible in the pigment epithelium (toluidine blue, ×1,000).

fragments and, after two hours in the fixative, the tissues were washed in Millonig buffer with 5.4% glucose. Postfixation was conducted for 30 minutes with 2% osmium tetroxide (Millonig buffer, pH 7.4). After washing, the tissues were dehydrated in ethanol and propylene oxide and embedded in Epon.

Sections were cut with diamond knives on a microtome (Reichert OMU 2), mounted on bare copper grids, stained with uranyl acetate and lead citrate, and photographed on a Philips EM 300 electron microscope.

Light microscopy—Lipid stains showed poorly contrasted material in the retinal ganglion cells. The trypsin digest preparations were normal.

By polarization microscopy, a marked birefringency was observed in the keratocytes, sclerocytes, and nonpigmented ciliary epithelium. It was less marked in the endothelial and epithelial cells of the cornea, and in the pigmented epithelial layers of the ciliary process and the pars plana. Birefringency was prominent in all the retinal ganglion, amacrine and Müller's cells, in the endothelial cells of most of the retinal, choroidal, and ciliary vessels, in the retinal pigmented epithelium, and in the fibrocytes of the choroid (Fig. 1).

The number of ganglion cells appeared normal in the retina. The optic nerve showed a severe diminution of the myelin sheaths with glial proliferation.

Electron microscopy—Electron microscopy showed that the storage material was present in the form of lamellar inclusions limited by a membrane. The lamellar inclusions varied in size from 0.2 to 3.0 μ. Recognizable were two distinct types of lipid cytosomes:

1. The first type of lipid cytosomes con-

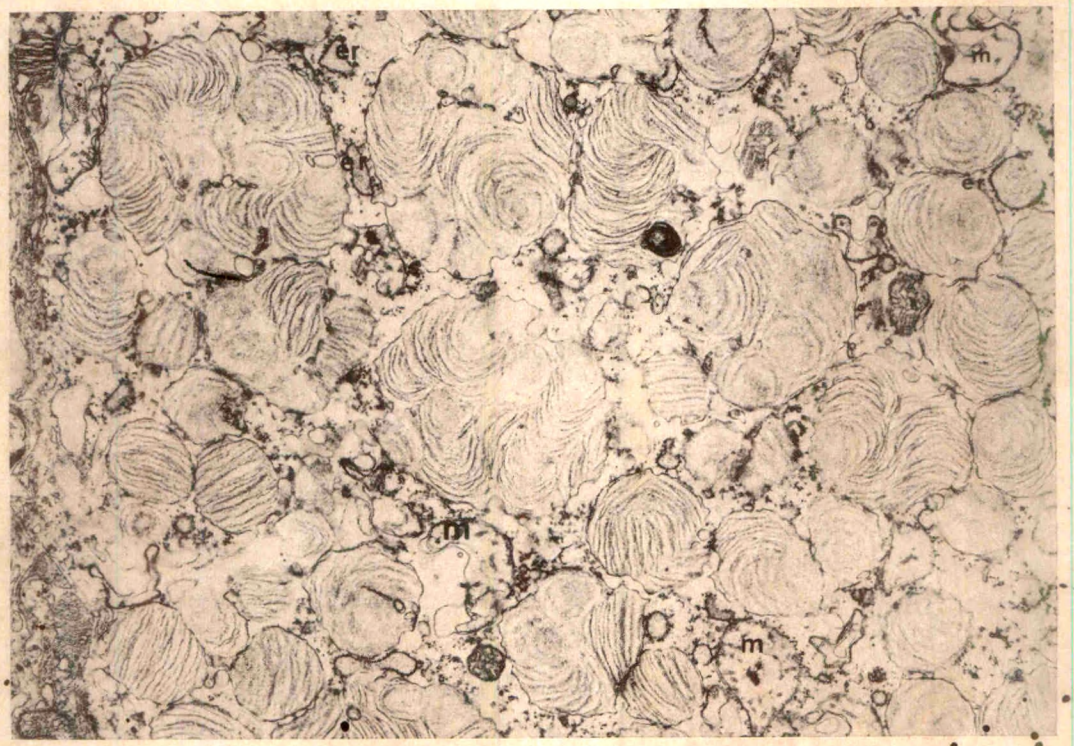


Fig. 2 (Libert, Toussaint, and Guiselings). Retinal ganglion cells. The cytoplasm is filled with poorly contrasted lamellar inclusions with evidence of coalescence. Mitochondria (m) and endoplasmic reticulum (er) are also evident (×17,100).

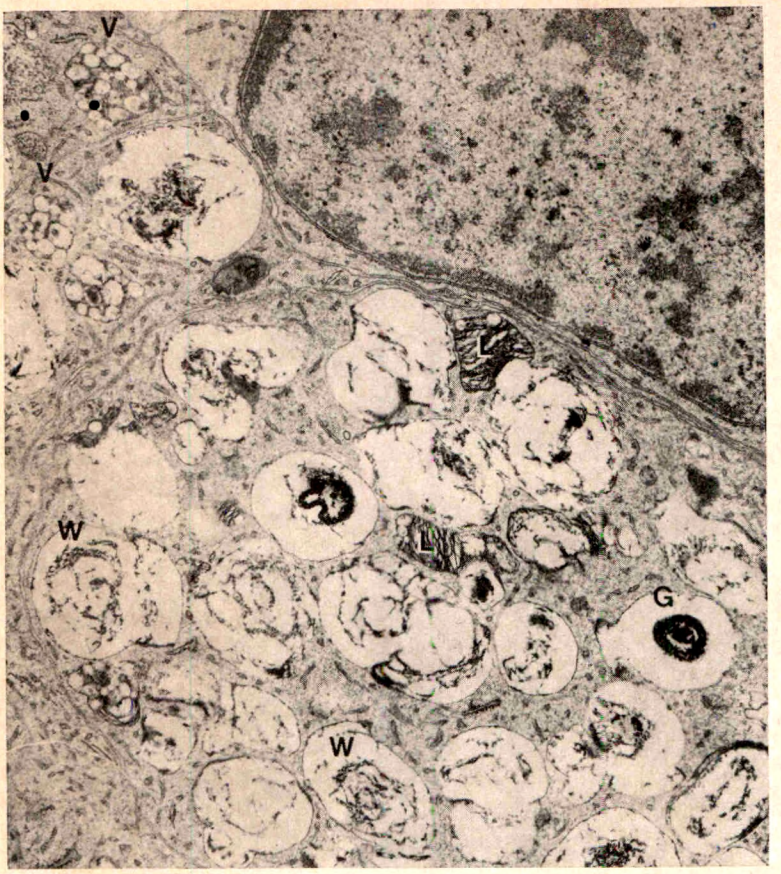


Fig. 3 (Libert, Toussaint, and Guiselings). Retina. Müller's cells show pleomorphic inclusions—lamellar (L), granular (G), vacuolated (V), or whorled (W)—with many transitional pictures. Electron-lucent areas often alternate with dense material (×16,100).

sisted of large parallel or concentrically laminated membranes that resembled the membranous cytoplasmic bodies of Tay-Sachs disease. These round inclusions showed poorly. Many appeared to be compressed and in the process of fusing together. The ganglion cells and the axons of the retina showed a striking profusion of this first type of membranous cytoplasmic bodies (Fig. 2). The cone and rod myoid and perikaryon, the bipolar and amacrine cells contained some of these inclusions.

2. The second type of lipid cytosome had a dense lamellar structure that was less uni-

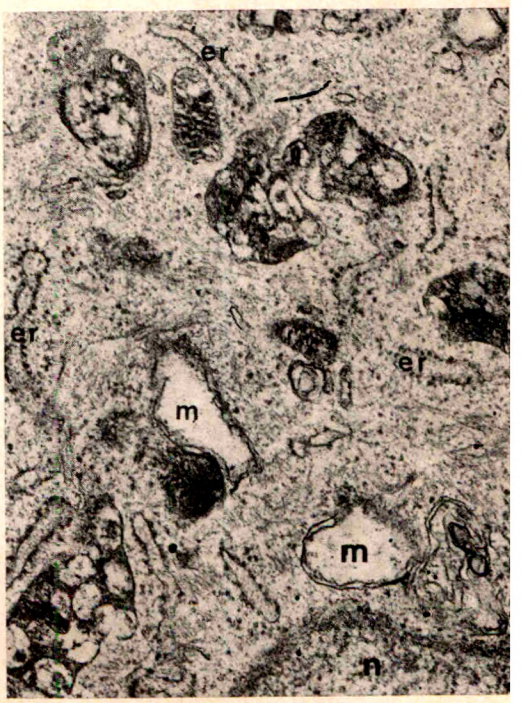


Fig. 4 (Libert, Toussaint, and Guiselings). Corneal epithelium. Dense lamellar or vacuolated inclusions are evident. Nucleus indicated by n; endoplasmic reticulum, er; and mitochondria, m (×35,370).

form than in the type 1 membranous cytoplasmic bodies. These inclusions were round, oval, or rectangular. Their architecture varied in the same tissue or even in the same cell, appearing granular, vacuolated, or whorled. Transitional forms were numerous (Fig. 3). Electron-lucent areas or dense homogenous material often alternated with irregular, dense lamellar structures. The lipid cytosomes of the second type were similar to those found in the liver or in the bone marrow of our patient.

The type 2 inclusion bodies were widely distributed. They were found in the conjunctival and corneal epithelial cells (Fig. 4), in the keratocytes (Fig. 5), in the connective tissue cells of the conjunctiva, in the ciliary muscles (Fig. 6), in the nonpigmented epithelium of the ciliary processes (Fig. 7), in the choroidal and iridic fibrocytes (Fig. 8), in the endothelial cells, and in the pericytes of the retinal and choroidal vessels (Fig. 9), as well as in the lymphocytes seen in the vessels.

The lamellar structures in the lens epithelium were well preserved. The Müller and glial cells in the retina contained type 2 inclusions with loosely arranged dense concentric membranes, which contrasted with the pale type 1 inclusions seen in the adjacent retinal neurons (Fig. 10). Many inclusions were found in the glial cells of the demyelinated optic nerve and in the Schwann's cells of the ciliary nerves (Fig. 11).

The pigmented epithelium of the iris and the choroidal and iridic melanocytes appeared normal (Fig. 8). The pigmented epithelium of the ciliary body and pars plana showed some inclusions that were similar to



Fig. 5 (Libert, Toussaint, and Guiselings). Corneal stroma. Keratocytes show well-preserved lamellar inclusions with periodicity of 5.5 nm (×70,000).

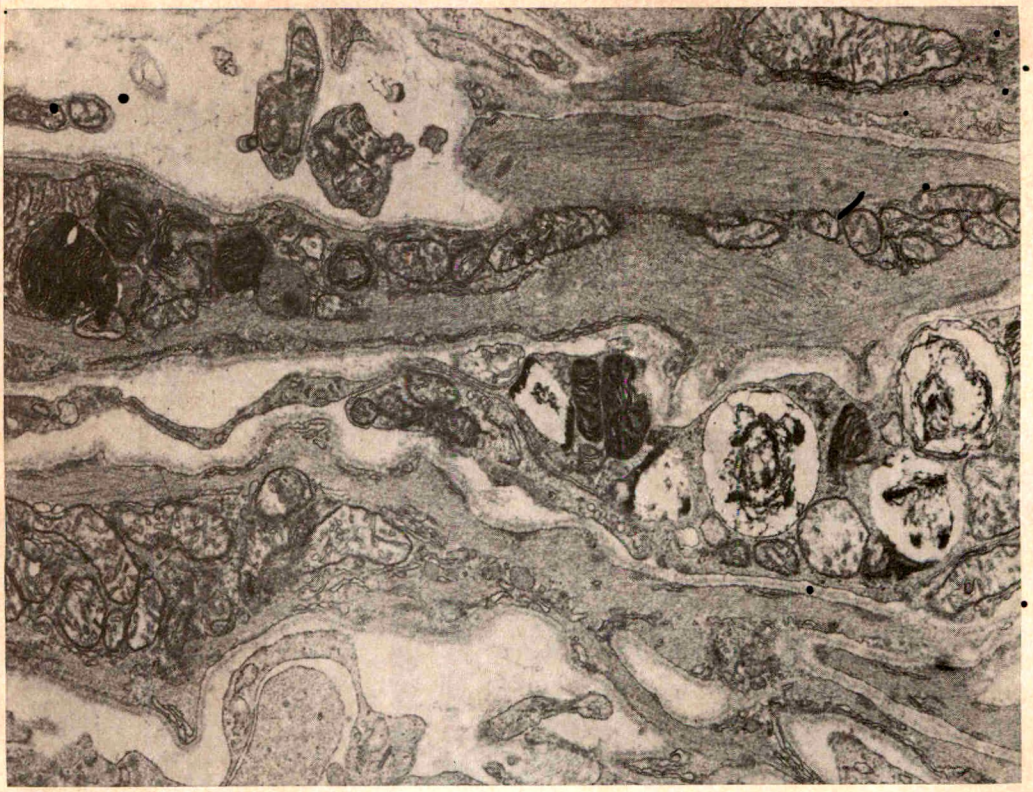


Fig. 6 (Libert, Toussaint, and Guiselings). Whorled or lamellar inclusions are evident in the fibers of the ciliary muscle among the mitochondria (×17,100).

those of the heavily involved nonpigmented epithelium. The storage process was prominent in the retinal pigment epithelium, which showed many forms transitional between phagocytozed outer segment material and type 2 inclusions (Fig. 12).

Discussion

The widely distributed lamellar inclusions, observed by electron microscopy, closely correspond to the sites of birefringency observed by polarization. The extent of the storage process is similar to that observed by Robb and Kuwabara[8] and explains the clinical ocular symptoms.

The pleomorphic type 2 inclusions showed a marked resemblance to those observed in biopsy specimens of the liver, the bone marrow, and the conjunctiva of our patient.[13] Other authors[14-20] also noted indentical inclusions in various tissues. Lejeune and associates[21] classified those inclusions into four types according to the successive stages in the degradation of lipid storage material. According to our findings, we would assign all these inclusions to the type 2 category. They are typical of Niemann-Pick disease and their structural characteristics, including the presence of hydrolytic enzymes,[22,23] prove their lysosomal nature. Their major components are sphingomyelin and cholesterol.[4,24]

The type 1 membranous cytoplasmic bodies resemble those described by Cogan, Kuwabara, and Moser[25] in retinal ganglion cells in cases of sulfatidosis, and by Garner[26] in Sandhoff's disease. Their lamellar architecture is less dense than in Tay-Sachs disease and in GM_1 gangliosidosis.[27,28] Similar inclusions have also been demonstrated in the retinas of patients with Hunter's syndrome.[29]

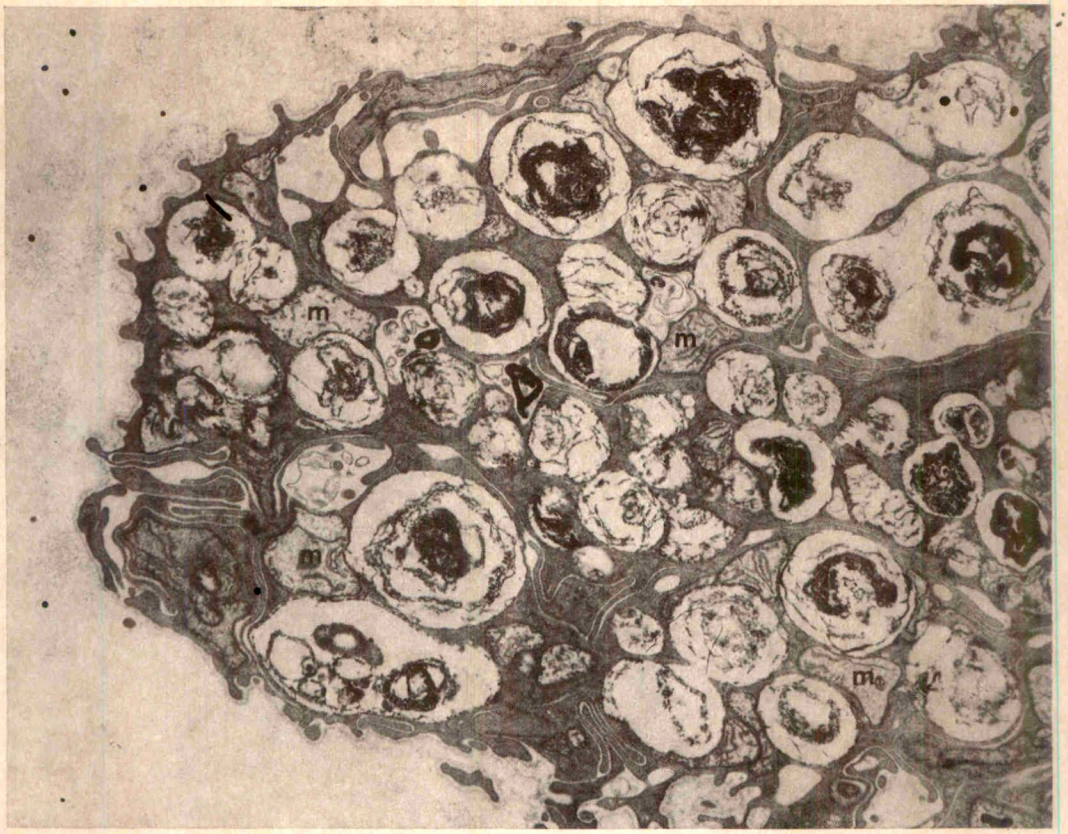


Fig. 7 (Libert, Toussaint, and Guiselings). Ciliary body. The nonpigmented epithelium is swollen by whorled inclusions. Mitochondria (m) (×10,530).

The occurrence of two different types of inclusions in neurons and in other cells in the lipidoses is not exceptional. Cogan, Kuwabara, and Moser[25] described aspecific inclusion bodies in the retinal ganglion cells in metachromatic leukodystrophy, in contrast to the typical prismatic inclusions found by other authors[30,31] in the Schwann's cells of



Fig. 8 (Libert, Toussaint, and Guiselings). Iris stroma. The fibrocytes (f) contain many lipid vacuoles contrasting with the unaffected melanocytes (m) (×11,400).

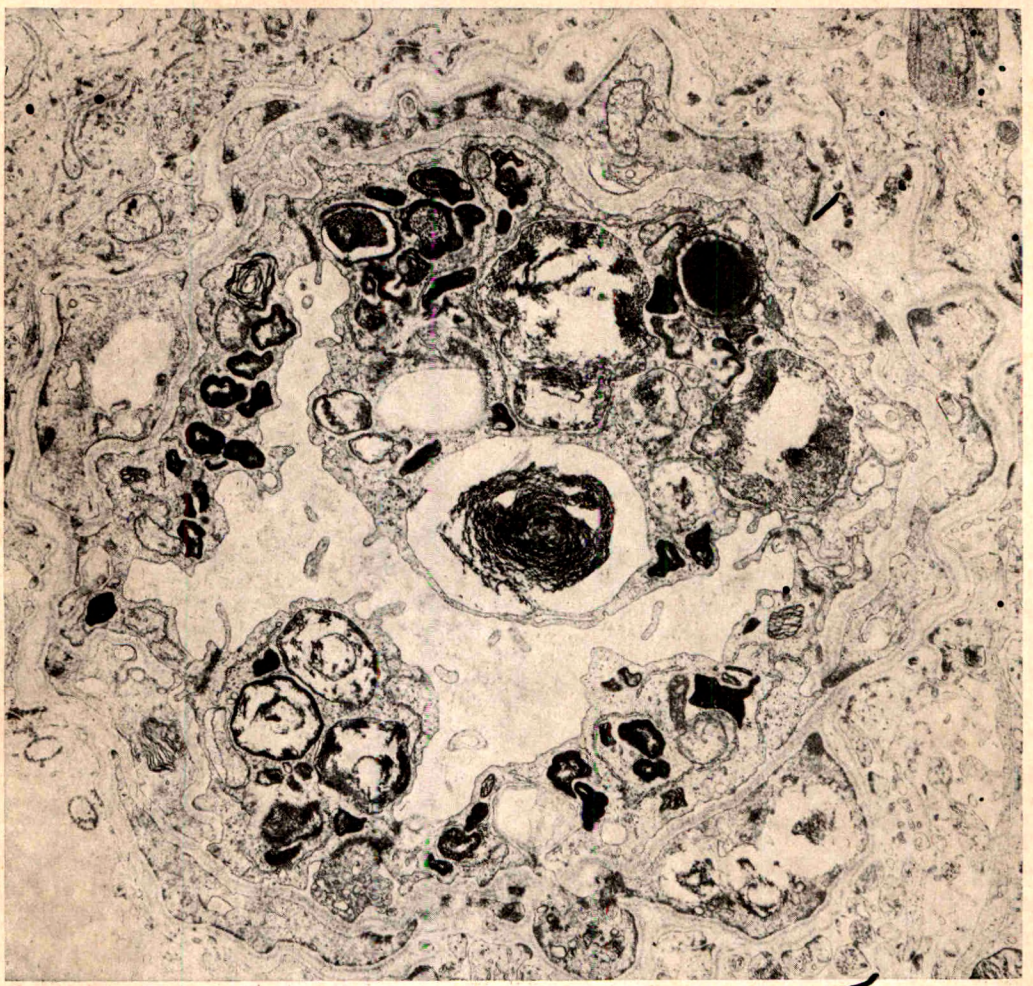


Fig. 9 (Libert, Toussaint, and Guiselings). Retinal vessel. Endothelial and mural cells are filled with pleomorphic type 2 inclusions (×19,380).

the ciliary nerves, the glial cells of the optic nerve, and in the brain. Emery and associates[28] observed membranous cytoplasmic bodies in the retinal ganglion cells in cases of G_{M1} gangliosidosis that differed from the inclusions seen in the other ocular structures, while Suzuki, Suzuki, and Chen[32] identified membranous cytoplasmic bodies in the cortical neurons that were entirely different from the inclusions in the adjacent glial cells. In Gaucher's disease, lamellar inclusions are found in the cerebral neurons, while specific Gaucher bodies are observed in other tissues.[33]

Several authors[14,19,33] who studied Niemann-Pick disease observed lipid cytosomes that correspond to our type 2 inclusions in the neurons and the glial cells of the brain. Adachi and associates[34] described lipid inclusions in the ganglion cells of the myenteric plexus, resembling the membranous cytoplasmic bodies of Tay-Sachs disease rather than the vacuoles found in the central nervous system and the liver. These lipid inclusions were markedly similar to our type 1 inclusions. In a given form of lipidosis, the morphologic differences in the abnormal inclusions may be related to variability of the metabolism in various cellular systems.

The pigment epithelium seems to be un-

affected in Tay-Sachs disease, Sandhoff's disease, metachromatic leukodystrophy, I-cell disease, and Maroteaux-Lamy syndrome.[25,27,30,35,36] It is also normal in the retina in G_{M1} gangliosidosis but contains occasional cytoplasmic vesicles similar to those of the unpigmented epithelium in the ciliary body.[28] Clear fibrillogranular vacuoles are found in the pigmented and nonpigmented epithelium of the ciliary body in Hunter's syndrome, while lamellar inclusions are present in the retinal pigment epithelium and in the ganglion cells.[29] Apparently, melanocytes are never involved in these metabolic diseases.

In our patient, the melanocytes and the pigmented epithelium of the iris were free of inclusions but the retinal pigment epithelium



Fig. 10 (Libert, Toussaint, and Guiselings). The ganglion cells (G) are swollen by poorly contrasted lamellar inclusions (type 1), while adjacent Müller's cells (M) contain loosely arranged dense material (type 2 inclusions) (×25,500).

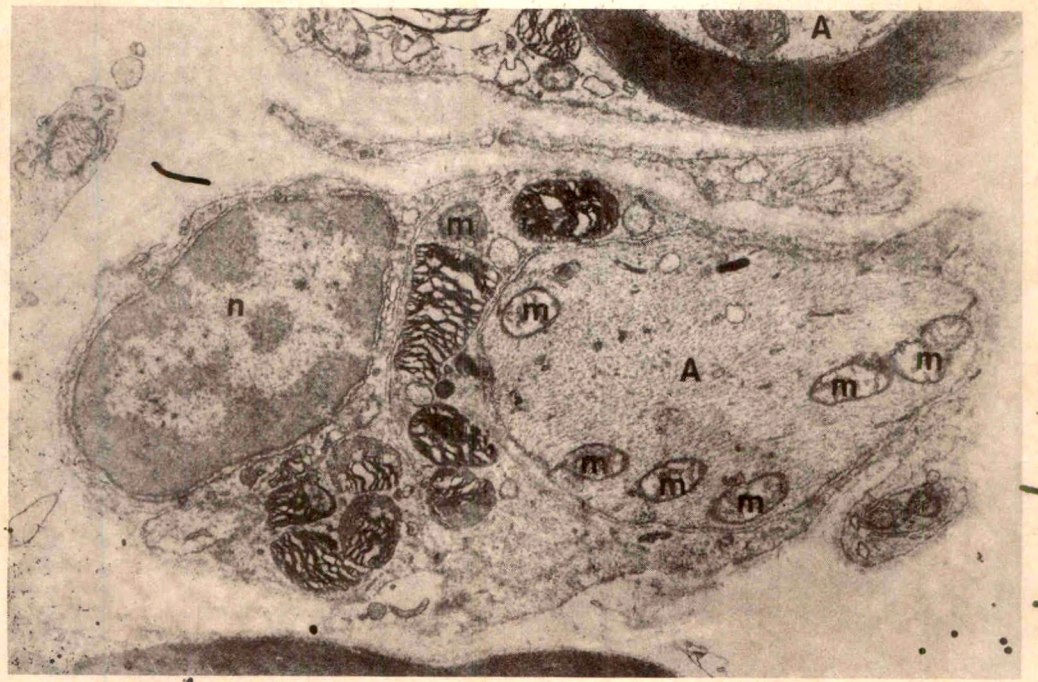


Fig. 11 (Libert, Toussaint, and Guiselings). Ciliary body. The Schwann's cells of the ciliary nerves show lamellar inclusions of type 2. Axon (A), nucleus (n), and mitochondria (m) are also evident (×17,510).

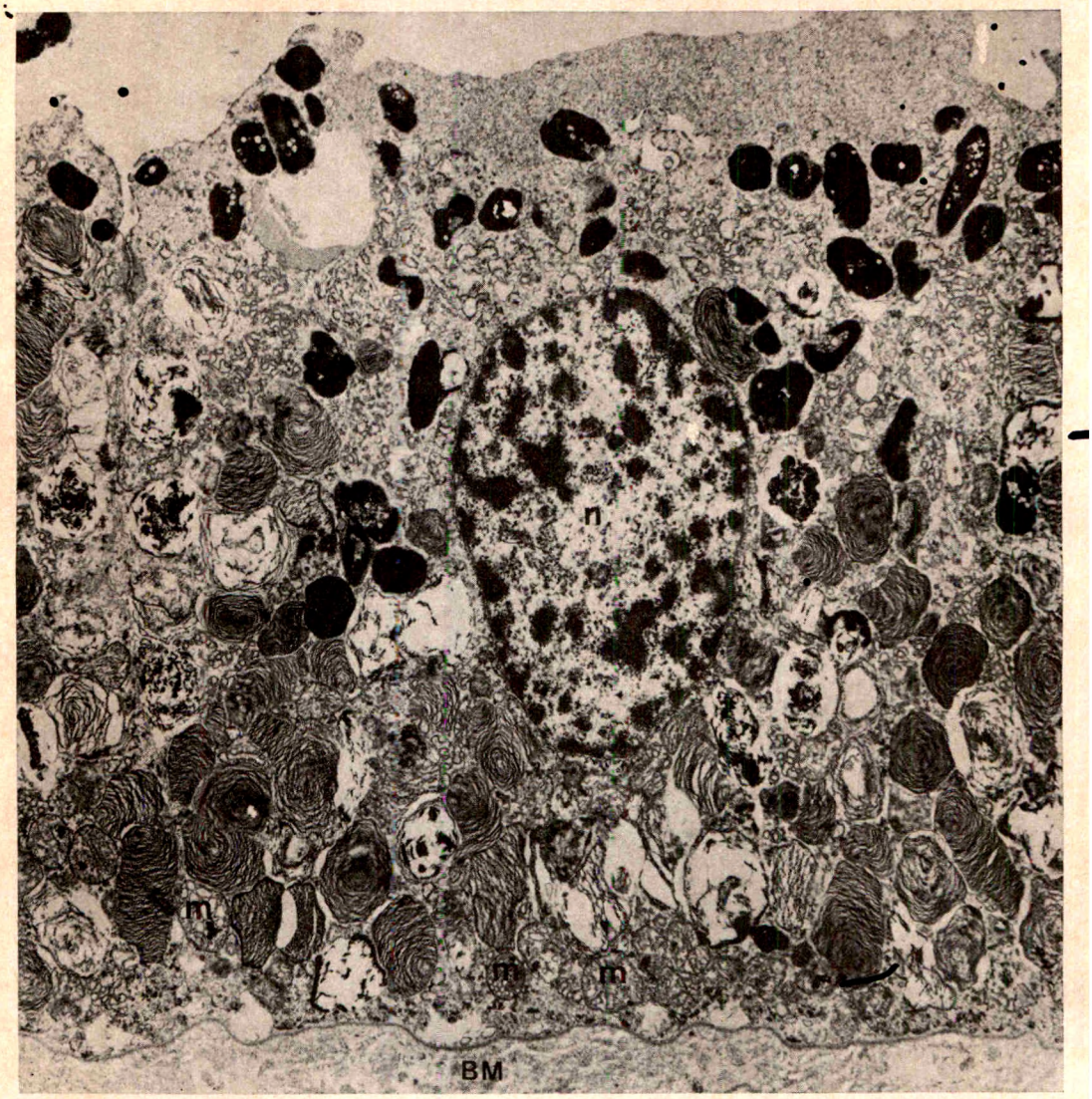


Fig. 12 (Libert, Toussaint, and Guiselings). Retinal pigment epithelium. The cells show a striking profusion of pleomorphic dense type 2 inclusions, and seems poor in pigment granules. Many transitional structures are seen between phagocytized outer segments and loosely arranged whorled material. Mitochondria (m), nucleus (n), and basal membrane (BM) are seen (×10,560).

was filled with lamellar inclusions, and the pigmented epithelium of the ciliary body and the pars plana contained several whorled inclusions identical to those of the heavily involved nonpigmented epithelium. This suggests that the storage process in pigmented cells is induced by the intimate contact with affected cells. The occurrence in the retinal pigment epithelium of many transitional structures between the outer segments and the lamellar or whorled inclusions may result from an inability to destroy this material because of the enzymatic defect.

Summary

Light and electron microscopic studies of the eyes of a 3½-year-old girl who died of Niemann-Pick disease disclosed accumulation of intralysosomal lipid material in all cells other than those that were pigmented.

The nonpigmented layer of the ciliary process and the ganglion cells of the retina were especially involved.

Electron microscopy revealed two main types of lipid cytosomes. The presumptive explanation for this finding is that the metabolism of the stored material in neurons differs from that in other cells.

Topographic and structural studies of the pathologic pigment epithelium suggested that pigmented cells show storage material either when they are in intimate contact with affected cells or when the enzyme defect interferes with the catabolism of the outer segments.

Acknowledgments

Dr. J. P. Hubert (University of Brussels) provided the ultrastructural study of the bone marrow and the liver, and Dr. G. Dacremont (University of Ghent) provided the determination of the sphingomyelin levels in serum and urine.

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Ophthalmic miniature

Science, as its lowliest, focuses on two elements, fact and ~~technic~~. Its intermediate phase centers on relations. Its highest level deals with scientific theories and cosmologies.

Edmond A. Murphy,
Clinical genetics: Some neglected facets,
N. Engl. J. Med. 458, 1975

ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY ASSOCIATED WITH AN ADENOVIRUS TYPE 5 INFECTION

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Acute posterior multifocal placoid pigment epitheliopathy is a rare disease thought to be an inflammatory reaction in either the retinal pigment epithelium or the choriocapillaris, or both.[1] Toxoplasmosis,[2] viruses,[1,3-5] tuberculosis, and erythema nodosum[6] have been suggested as possible etiologic agents, but the true cause has not yet been determined. We describe a patient who presented with the typical clinical and fluorescein angiographic findings of acute posterior multifocal placoid pigment epitheliopathy with positive viral cultures and rising antibodies to adenovirus type 5.

CASE REPORT

In March 1974, a 19-year-old black man was seen with complaints of painless loss of vision in both eyes of two weeks' duration. The patient first noticed a gradual loss in vision of the left eye over a period of several days, followed a week later by considerable loss of vision in his right eye, which then prompted his visit. He could not recall any similar previous occurrences, antecedent infectious episodes, or unexplained fevers, and there was no history of past trauma. He denied taking any medication. The family history was also negative.

Corrected visual acuity was 20/300 in each eye. Intraocular pressures were normal. A trace of flare and +1 cells were present in the anterior chamber. The positive findings were limited to both posterior poles where grayish-white lesions of irregular shape (¼ to ⅛ disk diameters) were scattered throughout the paramacular area but not involving either fovea. These lesions appeared to be subretinal on contact lens biomicroscopic examination (Fig. 1). Fluorescein angiographic study showed partial early blockage of fluorescein dye with late fluorescein staining of the lesions (Fig. 2).

Other than the visual loss, the patient was asymptomatic and in good physical health. Physical examination after hospitalization disclosed enlarged tonsils. Urinalysis, hemograms, and chest x-ray film results were normal. Bacterial cultures of blood, stool, and urine were negative. Skin tests for histoplasmosis, tuberculosis, coccidioidomycosis, and blastomycosis were negative. The urine was negative for cytomegalic inclusions. The VDRL and fluorescent treponemal antibody absorption (FTA) tests were nonreactive. Antibody tests for rubella, herpes zoster, herpes simplex, and toxoplasmosis with acute and convalescent sera showed no significant change in titer.

On the fifth hospital day the patient developed a low-grade fever, associated with inflamed tonsils, general malaise, and anorexia.

RESULTS

Blood was drawn on the first, eighth, and 60th day of observation for viral and bacterial cultures and antibody titers. Cultures of the throat were obtained on the fourth day and a tonsillar biopsy specimen was obtained on the seventh day (Table). Adenovirus type 5 was isolated from both the throat swab and from the homogenate of the tonsillar

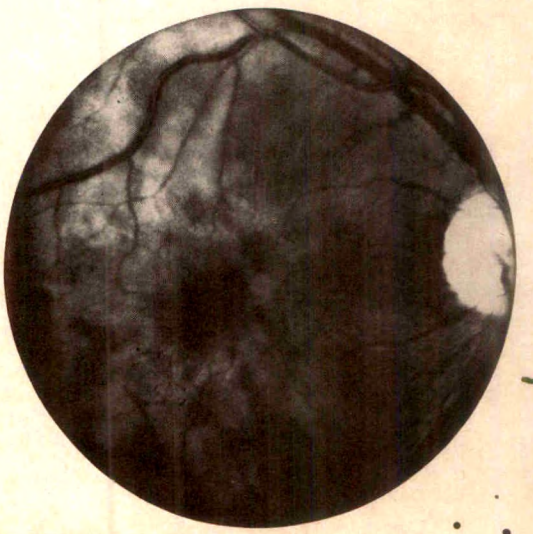


Fig. 1 (Azar and associates). Red-free photograph of right eye when patient was first seen; visual acuity, 20/300. Multiple grayish-white nondiscrete subretinal placoid lesions scattered throughout the posterior pole.

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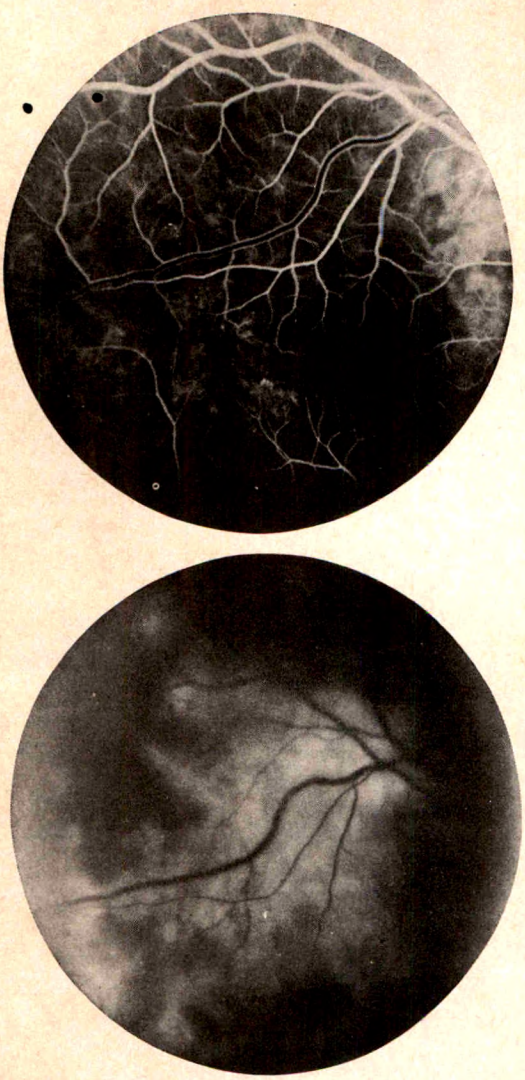


Fig. 2 (Azar and associates). Top, Early arteriovenous phase angiogram of right eye demonstrating multiple areas of choroidal nonfilling at locus of placoid lesions. Some retinal pigment epithelium is visible and may be secondary to the two to three weeks' presence of this disorder, explaining the absense of total blockage of dye in these zones. Bottom, Late phase (15 minutes) dye staining of placoid lesions.

biopsy tissue. Complement-fixation antibody tests for adenovirus type 5 were negative for blood drawn on the first and eighth days, but rose to 16 in the last specimen taken on the 60th day. Serum obtained on the eighth day had an adenovirus type 5 neutralizing antibody titer of less than 8; the titer rose to 32 after 60 days. The isolation of virus from two sources, accompanied by a serologic rise in antibody titer by two tests, provided firm evidence of adenovirus infection occurring concurrently with the acute phase of the patient's ocular disease.

The patient remained in the hospital for two weeks and received no medication during that time. On discharge, visual acuity was R.E.: 20/100, and L.E.: 20/30, and pigmentation had increased in the placoid lesions. Six weeks from the onset of the illness, visual acuity was 20/20 in each eye.

Six months later, the ophthalmoscopic examination showed multiple focal chorioretinal scars of the posterior pole at the exact loci of the prior acute placoid irregular lesions (Fig. 3).

Discussion

The ocular problems of this healthy young adult began with a marked decrease in visual acuity, first in one eye and then in both eyes. The ophthalmoscopic picture showed multiple circumscribed nonelevated subret-

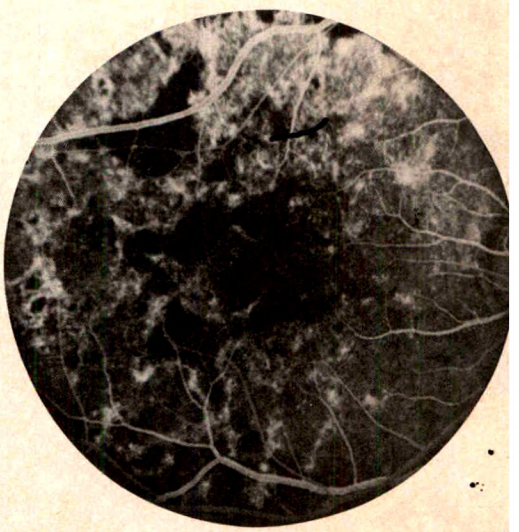


Fig. 3 (Azar and associates). Late arteriovenous phase angiogram of right eye six weeks later; visual acuity, 20/20, pigment clumping surrounding the macula with multiple zones of retinal pigment epithelium atrophy. The late phase of the angiogram (30 minutes) showed no evidence of late dye leakage.

TABLE

SUMMARY OF VIROLOGIC STUDIES

Date	Specimen	Result	Serology Titers	
			Complement Fixation	Neutralization with Adenovirus Type 5
3/8/74	Serum		Negative*	Negative*
3/11/74	Throat swab	Adenovirus type 5		
3/14/74	Tonsil biopsy specimen	Adenovirus type 5		
3/15/74	Serum		Negative	8
5/7/74	Serum		16	32

* Negative at serum dilutions of 1:8, the lowest dilution tested.

inal lesions, superficially resembling disseminated choroiditis. These early grayish-white plaque-like lesions changed in three to four weeks into depigmentations of the retinal pigment epithelium, with irregular clumping of pigment, and gradually progressed to inactive pigmented scars. The poor visual acuity dramatically resolved in six weeks after the onset of the disease.

During the acute phase partial blockage of early choroidal fluorescence was noted. We presume that the absence of total blockage of underlying fluorescence was because the lesion was not at its most acute form when first studied. The patchy nonfluorescence of the choroid may represent a delay in choriocapillaris perfusion or an isolated retinal pigment epithelial abnormality. The late phase angiography (15 minutes) of these same lesions showed definite fluorescein staining.

The cause of this form of pigment epitheliopathy is unknown. Viral disease has been suggested by several observers on clinical grounds alone.[1,3-5] Ryan and Maumenee[3] reported a viral-like syndrome accompanying acute posterior multifocal placoid pigment epitheliopathy in more than one half of their patients. In our study, viral isolation and serologic data indicate that an adenovirus type 5 infection occurred concurrently with the clinical syndrome of acute posterior multifocal placoid pigment epitheliopathy. This observation, considered with the reports of others, supports the thesis that a respiratory virus may be implicated in this disorder.

To our knowledge, ours is the second reported case occurring in a black person.[4]

SUMMARY

A 19-year-old black man with acute posterior multifocal placoid pigment epitheliopathy had concurrent positive viral cultures and rising antibodies to adenovirus type 5. This finding, considered together with earlier reports of viral-like syndromes accompanying the disease, supports the implication of a respiratory virus as a possible etiologic factor.

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OCULAR MANIFESTATIONS OF GAUCHER'S DISEASE

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There are two types of Gaucher's disease, an uncommon hereditary metabolic disorder —the adult and infantile forms. An accumulation of glucocerebroside in the reticuloendothelial organs, especially the spleen, liver, and bone marrow, characterizes the disorder. Although most reported cases have occurred in Jewish people, the disease may affect other ethnic and racial groups. The incidence in males and females is about equal.

We report the ocular abnormalities in a patient who had the clinical and laboratory findings of the adult type of Gaucher's disease.

Case report

A 27-year-old Gentile woman had had known hepatosplenomegaly for two years. One year before admission an extensive examination at another hospital had established no diagnosis. The present hospital admission was for progressive general weakness and a slow-growing mass in the region of the left flank. Her parents were healthy but a younger brother who had a verified case of the adult type of Gaucher's disease had undergone splenectomy (Fig. 1). Our patient's past medical history was unremarkable.

Physical examination showed a normal appearing young woman whose enlarged liver and spleen extended to the iliac crest. The skin of her legs showed a deep yellowish pigmentation. The remainder of the physical examination was unremarkable.

Ophthalmologic examination showed a visual acuity of 20/20 in each eye. The brownish globular masses on each side of the corneoscleral limbus of each eye resembled pingueculae (Fig. 2). The masses were granular, triangular, and brownish yellow. Yellowish infiltration of the bulbar conjunctiva extended for a short distance into the adjacent cornea at the level of Bowman's membrane. Ocular movements and visual fields were full. The fundi showed normal disks and vessels. In the left fundus, however, there was a peculiar lesion, about 1 disk in diameter, temporal to the macula (Fig. 3). The margins of the lesion were distinct, and the temporal edge was pigmented.

Laboratory studies showed the following values: red blood cell count, 4,000,000/mm³; hemoglobin level, 12.2 g/100 ml (76%); hematocrit reading, 36%; white blood cell count, 7,000/mm³; platelet count, 40,000 to 50,000/mm³; platelet functions and coagulative factors were normal; bleeding and clotting times were normal; serum alkaline phosphatase, 6 units/100 ml; serum acid phosphatase, 8 King-Armstrong units/100 ml; total serum bilirubin, 0.75 mg/100 ml; direct reacting serum bilirubin, 0.30 mg/100 ml; total serum proteins, 7.8 g/100 ml; serum albumin, 4.7 g/100 ml; serum globulins, 3 g/100 ml; transaminase glucomatic, 15 units; and pyruvic, 20 units. The following values were normal or negative: fasting blood glucose, creatinine, sodium, potassium, calcium, phosphorus, cholesterol, chest x-ray films, serology Kahn, and roentgenologic bone survey. Bone-marrow aspiration showed normal erythroid hyperplasia and infiltration by Gaucher's cells (Fig. 4). The biopsy of the pingueculae showed normal epithelium but beneath the epithelium there were areas of infiltration by Gaucher's cells.

Discussion

The clinical picture of Gaucher's disease varies considerably with the age of onset. Gaucher first described the adult type in 1882.[1] This most common and relatively benign type is characterized by splenomegaly, hematologic abnormalities, bone lesions, and conjunctival pigmentation. There are also alterations in the serum immunoglobulins.

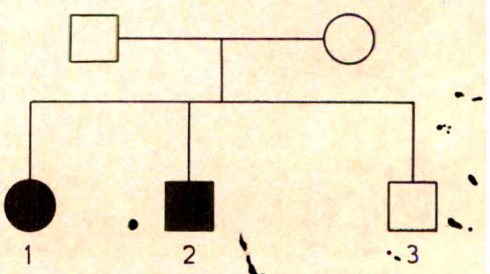


Fig. 1 (Petrohelos and associates). Pedigree of family with Gaucher's disease (affected male, solid square; affected female, solid circle).

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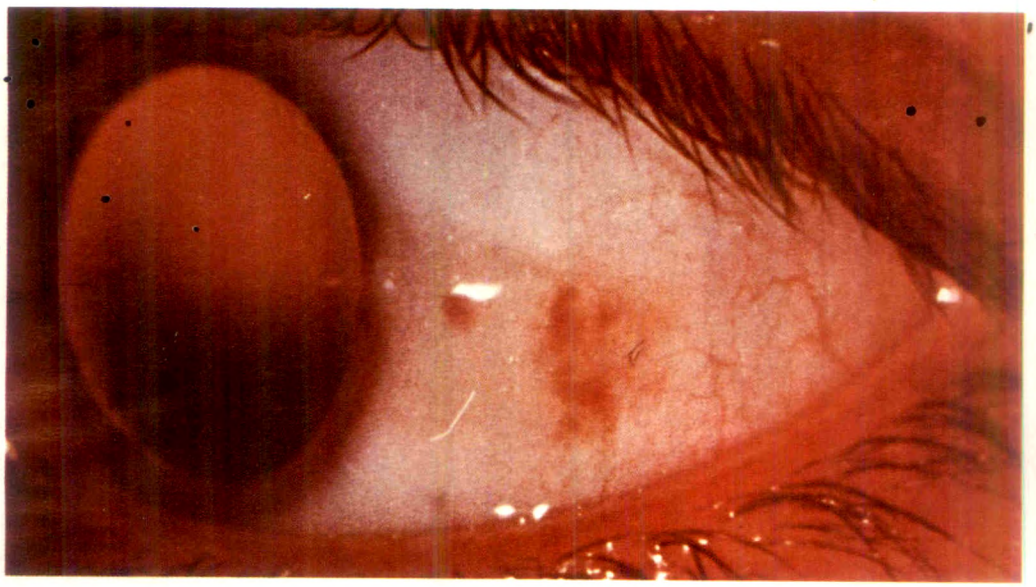


Fig. 2 (Petrohelos and Associates). The brownish pigmentation of the conjunctiva resembles pinguecula.

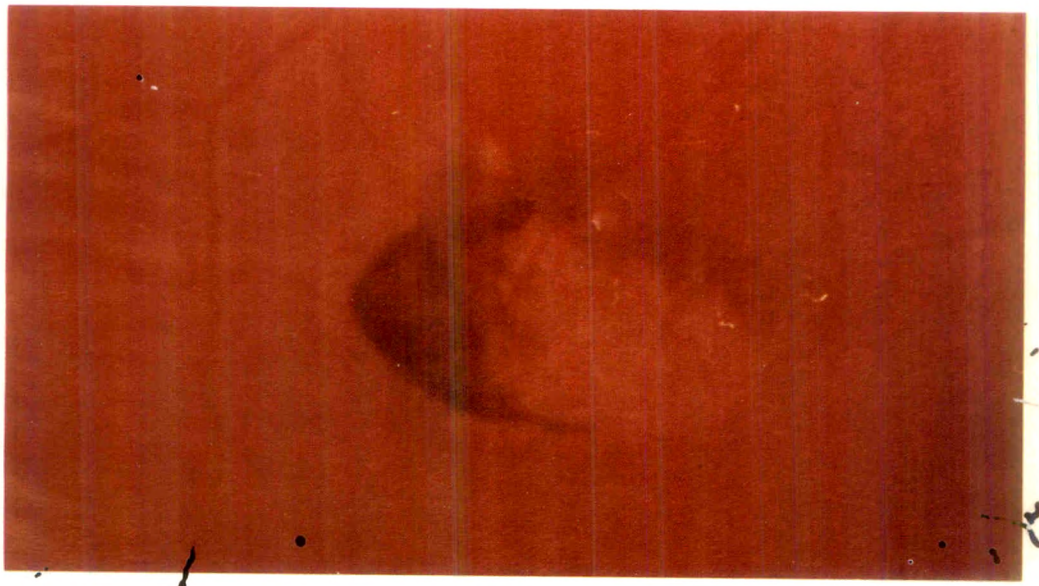


Fig. 3 (Petrohelos and Associates). Fundus photograph of patient with Gaucher's disease showing perimacular lesion.

In the infantile type, also called malignant or cerebral, the child is normal at birth but progressive retardation of development becomes evident at the age of 4 to 6 months. Although hepatosplenomegaly enlarges the abdomen, mental retardation and such neurologic signs as retroflexion and opisthotonos dominate the clinical picture. Skin and conjunctival pigmentation are absent in this form. Death usually occurs before the age of 2 years. Although the histologic and histochemical findings are similar in the two types of Gaucher's disease, organ involvement is more widespread in the infantile type.

In most families, transmission of both adult and infantile Gaucher's disease is consistent with autosomal recessive inheritance. However, the condition has been reported in successive generations in a few families.[2,3] The etiology of Gaucher's disease is still obscure. The cells characterizing it are formed by the storage of glucocerebroside within the cytoplasm of reticulum cells. Although Hibbs and associates[4] demonstrated a defect in glucocerebroside metabolism in Gaucher's disease, little is known of the mechanism by which glucocerebroside accumulates in Gaucher's cells where it forms characteristic tubular structures. An inherited enzymatic defect responsible for the degradation of cerebroside may be the underlying cause.

There is no known treatment for infantile Gaucher's disease. In the adult type, splenectomy may be performed to overcome the symptoms of hemolytic anemia or thrombocytopenia, or to relieve the discomfort caused by a huge spleen.

The typical ocular lesion of Gaucher's disease is a cuneiform or triangular thickening of the bulbar conjunctiva that appears on both the nasal and temporal sides of the corneoscleral limbus during the second decade of life.[5,6] The brownish lesion superficially resembles pinguecula. Histologically, however, it contains characteristic Gaucher's cells.[7,8] These conjunctival changes are almost pathognomonic of Gaucher's disease.

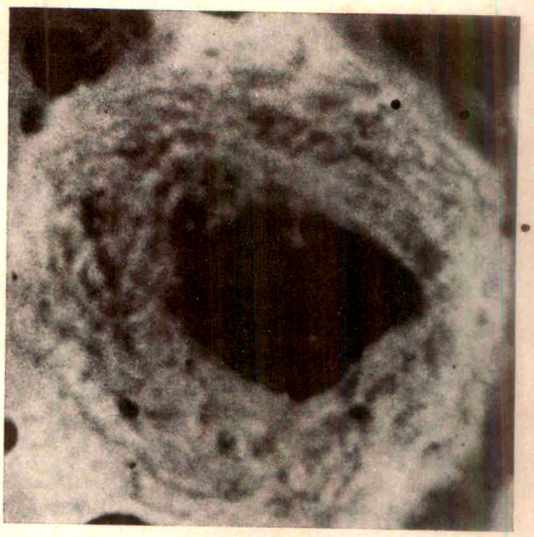


Fig. 4 (Petrohelos and associates). Typical Gaucher's cell in bone marrow (×2,000).

Histologic examinations of the choroid[9] have also disclosed Gaucher's cells.

Retinal hemorrhages, edema, nystagmus, and impaired abduction are associated with the anemia, and are more frequent in juveniles.[5,10] Occasionally, a red spot in the macula,[10] ring-shaped granular opacities around the fovea,[11] and perimacular degeneration[12,13] have been seen.

Summary

A 27-year-old woman not only had the usual clinical and laboratory features of the adult form of Gaucher's disease but also had typical pingueculae and a peculiar lesion with a pigmented temporal edge in the fundus of her left eye. Bone-marrow aspiration demonstrated infiltration by Gaucher's cells and a biopsy of the conjunctival masses disclosed areas of infiltration by Gaucher's cell beneath normal epithelium.

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Ophthalmic miniature

I observe the Phisician, with the same diligence, as hee the disease; I see hee feares, and I feare with him: I overtake him, I overrun him in his feare, and I go the faster, because he makes his pace slow; I feare the more, because he disguises his fear, and I see it with the more sharpnesse, because hee would not have me see it. He knowes that his feare shall not disorder the practise, and exercise of his Art, but he knows that my fear may disorder the effect, and working of his practise.

John Donne, 1623
Frank J. Warnke, ed.
John Donne: Poetry and Prose
New York, Random House, 1967

RHABDOMYOMA OF THE ORBIT

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Henderson[1] has questioned the existence of orbital adult-type rhabdomyoma, a benign tumor of well-differentiated striated muscle; his comprehensive and critical review of orbital tumors failed to uncover a single example at the Mayo Clinic or a well-documented published case. The most recent report of orbital rhabdomyoma by Nath and associates[2] is not unequivocal and prompts reservations, as do earlier case reports[3-6] that are poorly characterized and appear to be inflammatory pseudotumors involving the extraocular muscles or tumors other than rhabdomyoma. The present case of orbital rhabdomyoma is to our knowledge the first to be documented.

CASE REPORT

In July 1938, an 8-year-old white boy had a three-month history of an asymptomatic, gradually enlarging mass in the nasal aspect of his left upper eyelid. The mass was firm, circumscribed, nontender, and nonfluctuant, measuring 3 × 2 cm (Fig. 1). It extended from the inner canthus upward and backward, passing behind the orbital margin. It was not adherent to the overlying skin, but was not freely movable either. Visual acuity was 20/20 bilaterally and extraocular motility was undisturbed. The clinical diagnosis was hemangioma. At surgery, an encapsulated and multilobulated mass was found, arising from the anterior aspect of the belly of the medial rectus muscle. It extended superiorly to incorporate the trochlea. The mass and involved trochlea were locally excised.

Before the patient left the hospital, his mother noted a small, red carneous tag of tissue near the semilunar fold. This gradually increased in size, until four months later when the patient returned with a pea-sized lesion overlying the insertion of the medial rectus muscle (Fig. 2). This neoplasm was interpreted as a recurrent rhabdomyosarcoma, and an orbital exenteration was performed. The patient was alive and free of disease 27 years later (1965) but has since been lost to follow-up.

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RESULTS

Pathologic findings—Grossly, the lesion was described as a firm, bosselated, grayish-yellow, encapsulated mass, 3.3 × 2.0 × 1.5 cm that involved the trochlea (Fig. 3). Microscopically, the tumor was encapsulated but subdivided by thick fibrous septa into distinct lobules (Figs. 4 and 5) and composed of compactly arranged, large, round to polygonal cells with abundant granular, acidophilic cytoplasm (Fig. 6). High magnification disclosed that the granular nature of the cytoplasm was due to the presence of numerous myofibrils oriented haphazardly in three dimensions. Degenerating tumor cells displayed brilliant fuchsinophilia due to compaction of the myofibrils in the shrunken cytoplasm (Fig. 7). The myofibrillar nature of the cytoplasm of the cells was well demonstrated by the trichrome stain.

Each cell generally had a single, eccentrically placed, large, vesicular nucleus with

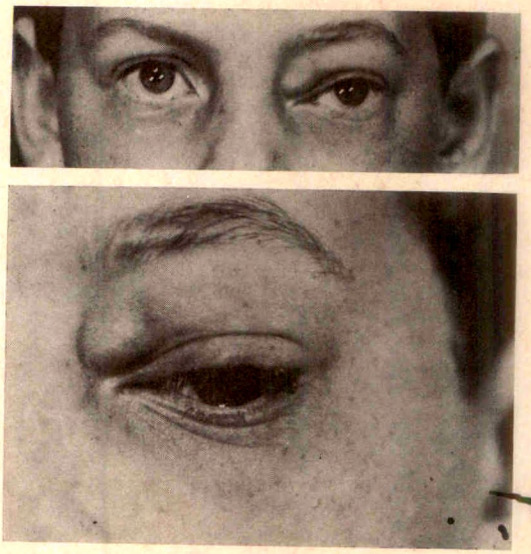


Fig. 1 (Knowles and Jakobiec). The tumor presented initially as a swelling in the upper nasal quadrant of the left orbit. No extraocular motility disturbances were noted.

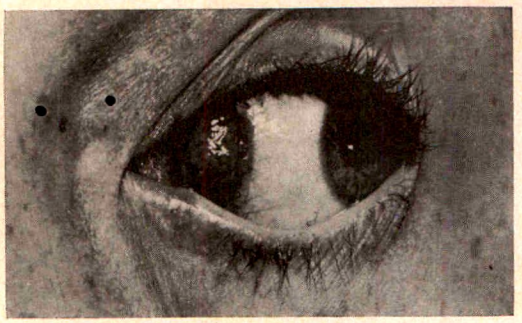


Fig. 2 (Knowles and Jakobiec). Four months later the tumor recurred at the insertion of the medial rectus muscle, presumably due to incomplete local excision initially.

a prominent, central, basophilic nucleolus (Fig. 6). Some cells had centrally placed nuclei or more than one nucleus. Many of the cells contained much glycogen, causing an apparent strand-like separation of the cytoplasm from the sarcolemma, suggesting large empty spaces with the formation of spider cells (Fig. 8). Sedulous microscopic examination showed cells with well-organized cross striations (Fig. 9). There were many cells with multiple, acidophilic, rod-like structures, so-called "myosin crystals" (Fig. 10).

Comment—We discovered this case of adult-type rhabdomyoma during our review of rhabdomyosarcomas on file here. The case was misdiagnosed as a rhabdomyosarcoma in 1938, before the diagnostic criteria for rhabdomyosarcoma and rhabdomyoma had been clearly established. Jones, Reese, and Kraut[7] described this patient in a series of orbital rhabdomyosarcoma cases (Case 14) in 1966.

Discussion

Rhabdomyomas most commonly occur in the hearts of infants, and are often associated with tuberous sclerosis.[8] The extracardiac rhabdomyoma, a benign tumor of

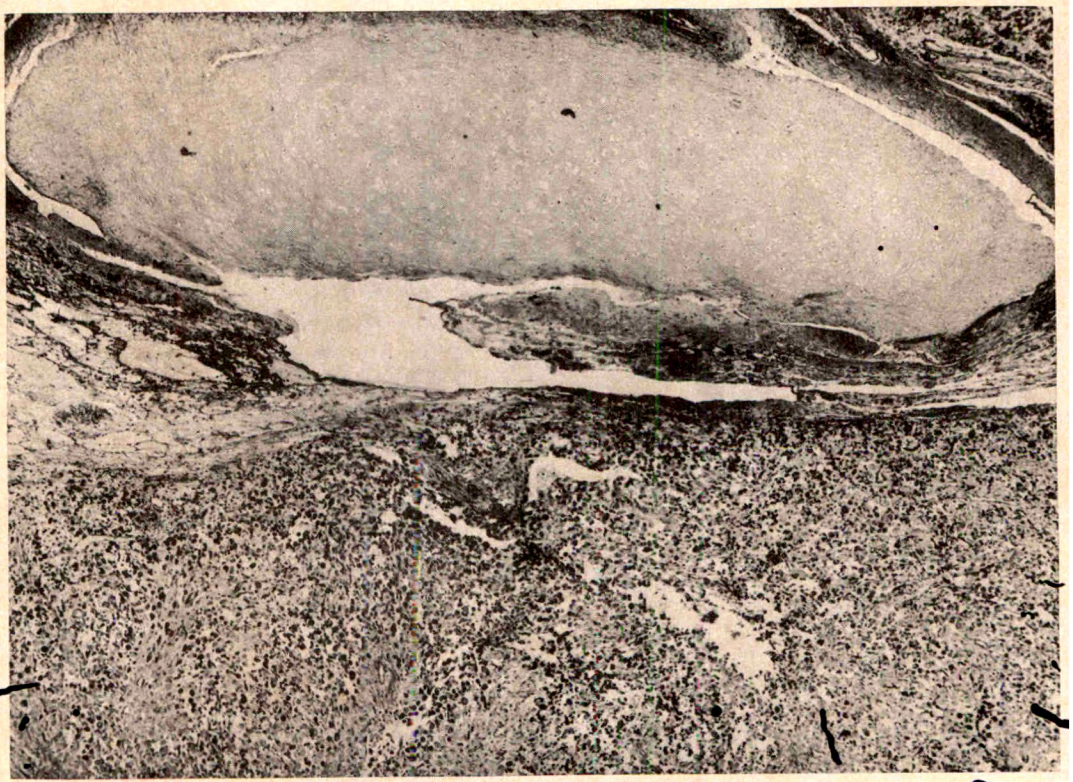


Fig. 3 (Knowles and Jakobiec). The trochlear cartilage is seen at the top with the tumor mass below it, separated by connective tissue with extravasated blood (hematoxylin and eosin, ×38).

striated muscle origin, is rare and, until recently, was one of the least understood human neoplasms. The confusion in older published reports stemmed from the all-inclusive diagnostic category of rhabdomyoma that encompassed numerous benign and malignant neoplasms containing striated muscle elements, for example, sarcoma botryoides, embryonal rhabdomyosarcoma, gonadal tumors, nephroblastomas (Wilms tumor), and mesenchyomas.[8]

Eleven years ago Moran and Enterline[8] extensively reviewed the nonophthalmic literature and found only 11 true extracardiac rhabdomyomas, adding a case of their own. Calhoun and Reese,[9] in their review of orbital myogenic tumors to 1942, accepted as benign tumors of fully developed striated muscle (rhabdomyomas) the cases of Jennings,[3] Alt,[4] and Wible.[5] Since then, two additional orbital rhabdomyomas were reported by Forrest[6] and Nath and associates.[2]

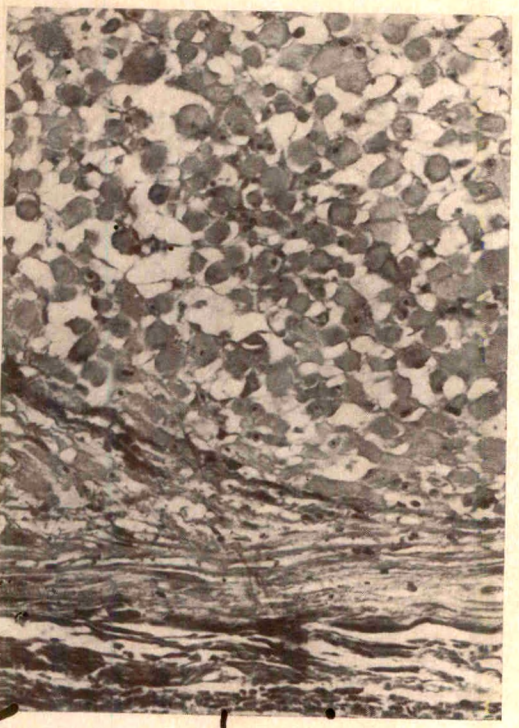


Fig. 4 (Knowles and Jakobiec). Note the thick connective tissue capsule (bottom) that embodies the tumor, outside of which lies extraocular muscle. A thin septum traverses the tumor, emphasizing its multilobular nature (trichrome, ×160).



Fig. 5 (Knowles and Jakobiec). The thick capsular border of the tumor is at the top (arrows). A fibrous septum traverses the tumor, dividing it into two distinct lobules. Such multilobulation may be responsible for an incomplete excision (trichrome, ×69).

Of the rhabdomyomas accepted by Calhoun and Reese,[9] those of Jennings[3] and Alt[4] lack adequate clinical and follow-up data. The histopathologic descriptions are not those of rhabdomyoma and photographic documentation is lacking. The case reported

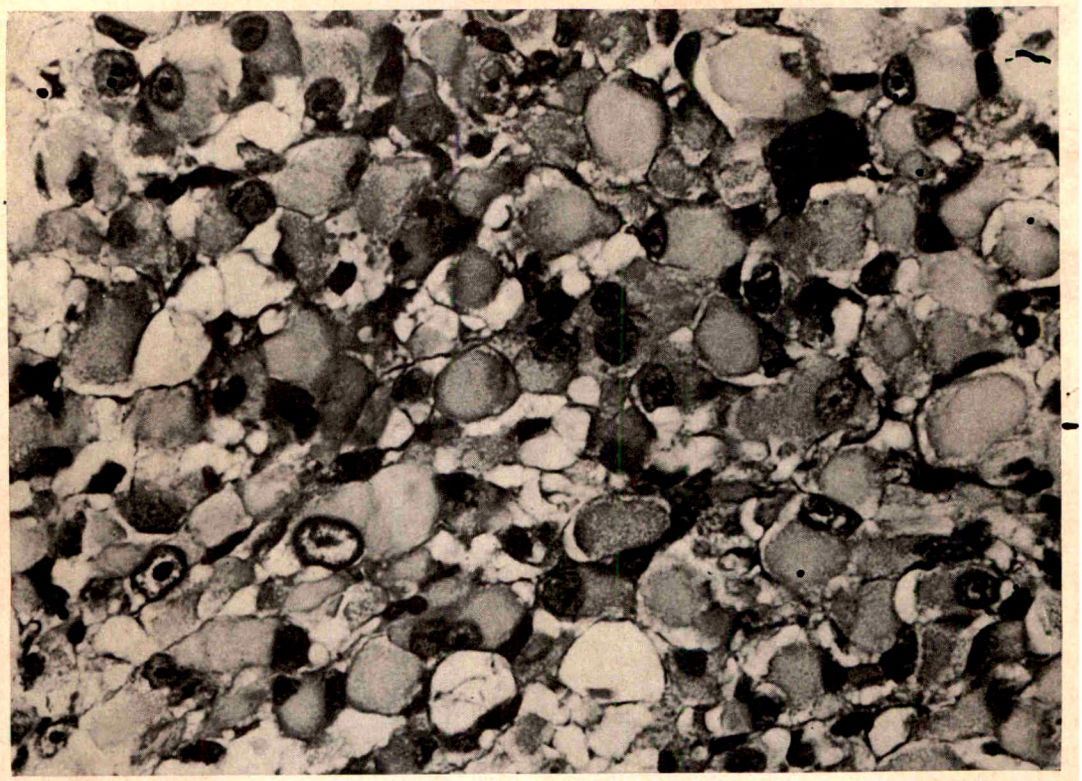


Fig. 6 (Knowles and Jakobiec). Rhabdomyoma is composed of large, round to polygonal cells with acidophilic, granular cytoplasm and large, vesicular, peripherally placed nuclei (trichrome, ×375).

by Wible[5] in 1918 was considered to be a sarcoma clinically and the microscopic diagnosis was rhabdomyoma, a term often used synonymously with rhabdomyosarcoma at that time. Wible did not provide a histologic description of the tumor or photomicrographs. Forrest[6] recorded a single rhabdomyoma in a group of 222 orbital neoplasms. His clinical and pathologic descriptions are sketchy and the single published photomicrograph may be consistent with a rhabdomyoma but is not diagnostic. The most recent report by Nath and associates[2] is also not unequivocal. Their description of abundant fibrous tissue and inflammatory cells located between striated muscle elements more probably describes a pseudotumor with residual adult striated muscle fibers in varying stages of degeneration. Their published photomicrographs support the latter interpretation. In summary, these five cases[2-6] lack, in whole or in part, adequate clinical, descriptive, and photographic documentation to be unequivocally accepted as rhabdomyomas.

Adult-type rhabdomyoma is distinctive among neoplasms displaying striated muscle differentiation. Neoplasms of striated muscle origin particularly relevant to this entity include, in ascending order of their differentiation toward normal adult striated muscle, embryonal rhabdomyosarcoma, fetal rhabdomyoma, and pleomorphic rhabdomyosarcoma, with adult rhabdomyoma as the best differentiated.

Embryonal rhabdomyosarcoma is a poorly differentiated, malignant spindle-cell neoplasm, usually displaying only subtle degrees of differentiation toward striated muscle. This neoplasm occurs most commonly in the head and neck region of children and is overwhelmingly the most common type of orbital rhabdomyosarcoma.[7,8]

Embryonal rhabdomyosarcoma almost always originates in the orbital soft tissues,[11] presumably from pluripotential embryonic mesenchyme possessing the capacity to differentiate into striated muscle.[12]

Dehner, Enzinger, and Font[13] described the fetal rhabdomyoma, a clinically benign but cytologically less mature variant of the adult-type extracardiac rhabdomyoma reported here. Most of these cases occur in children less than 3 years of age and arise in the subcutaneous tissues of the head and neck region (no orbital fetal rhabdomyomas have been reported). The histologic picture of fetal rhabdomyoma is strikingly different from that of the adult-type rhabdomyoma. Fetal rhabdomyomas consist of haphazardly arranged, irregular bundles of immature skeletal muscle fibers coexisting with a second population of small, oval to spindle-shaped, undifferentiated but benign-appearing mesenchymal cells.[13]

Pleomorphic rhabdomyosarcoma is a malignant neoplasm of striated muscle origin, with manifest striated muscle differentiation, that most commonly occurs in the peripheral skeletal musculature of adults.[10] Pleomorphic rhabdomyosarcoma has originated in the orbit; as expected an older patient population has been affected (21 to 78 years of age).[14,15] Unlike orbital embryonal rhabdomyosarcoma, orbital pleomorphic rhabdomyosarcoma seems to originate in the muscle belly of one of the extraocular muscles.[10,14,15] Thus, fetal rhabdomyoma may be regarded as the benign counterpart of embryonal rhabdomyosarcoma and adult rhabdomyoma as the benign counterpart of pleomorphic rhabdomyosarcoma.

The rhabdomyoma in this patient is a benign neoplasm, composed of mature but disorganized striated muscle fibers. Although called adult—in contradistinction to fetal rhabdomyoma which is also a benign neo-

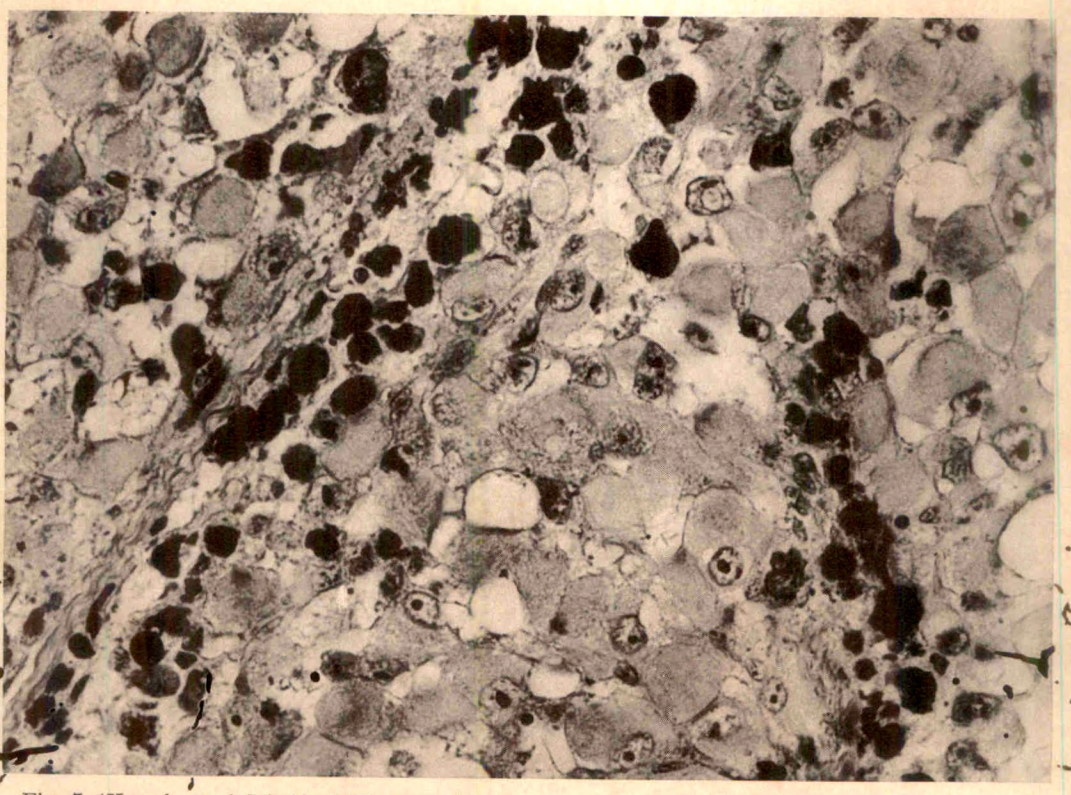


Fig. 7 (Knowles and Jakobiec). Degenerating tumor cells show intense fuchsinophilia due to compaction of the myofibrils in the shrunken cytoplasm (trichrome, ×375).

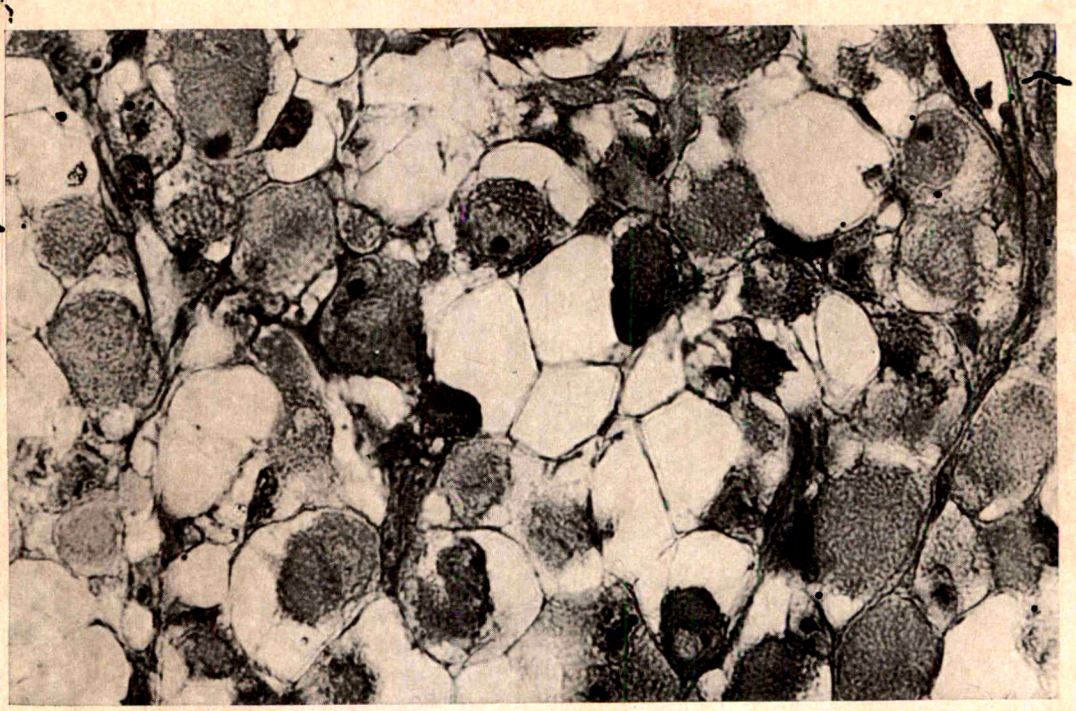


Fig. 8 (Knowles and Jakobiec). Occasional cells contain large amounts of peripherally placed glycogen, resulting in apparent strand-like retraction of the cytoplasm from the sarcolemma and the formation of spider cells (trichrome, ×375).

plasm but has an appreciable admixture of primitive cells—this well-differentiated type of rhabdomyoma may develop in childhood, as in the present case. Like its malignant counterpart, the pleomorphic rhabdomyosarcoma, rhabdomyoma occurs only rarely in the orbit but when it does occur there, it also originates in one of the extraocular muscles. Similarly, the extraorbital adult rhabdomyomas have generally originated in regions where striated muscle fibers abound, that is, tongue, larynx, pharynx, subcutaneous tissues of the head and neck, or rarely in a muscle belly.[8,16,17] To the best of our knowledge, there has never been an instance of a rhabdomyosarcoma originating in, or associated with, a rhabdomyoma.

Ultrastructural studies of several nonorbital rhabdomyomas with similar histology to the case reported here demonstrated that most of the tumor cells exhibit the cytoarchitecture of striated muscle cells: numerous thick and thin myofilaments frequently forming rudimentary sarcomeres randomly disposed throughout the cytoplasm, mitochondria, glycogen, elements of the T-system (smooth surfaced cisternal profiles), and rough surfaced endoplasmic reticulum. Focally thickened and modified Z-band material in elongated rod-like formations probably accounts for the myosin crystals frequently identified with the light microscope and demonstrated in the present case (Fig. 10).[16-18] Cornog and Gonatas[18] described the presence of typical satellite cells of skeletal muscle in a retropharyngeal rhabdomyoma.

Scrutiny of published reports of rhabdomyoma shows that most patients were treated by local excision of the tumor mass with a small rim of uninvolved surrounding tissue; not a single instance of recurrence has been documented in any of these cases. In this patient the recurrence was misinterpreted as a sign of malignancy but was doubtlessly due to failure to excise fully all of the lobulations at the first operation, one

of which served as the nidus of the recurrence.

The progenitor cell of tumors originating from or in striated muscle is not known. A dedifferentiation of essentially end-stage, nonreplicative, mature striated muscle fibers appears less likely than an origin from an undifferentiated or uncommitted mesenchymal cell capable of striated muscle differentiation. In this regard, Cornog and Gonatas[18] described the presence of typical skeletal muscle satellite cells in their ultrastructural study of a pharyngeal rhabdomyoma. The normal satellite cells are nondescript, primitive cells that are closely applied against skeletal muscle fibers at various intervals along their length and that are enclosed within their basement membranes.[19] Some investigators[19-22] concluded that satellite cells play an important role in muscle embryogenesis and muscle regeneration; they may also be responsible for such aberrant proliferations as fetal rhabdomyoma, adult rhabdomyoma, and pleomorphic rhabdomyosarcoma.



Fig. 10 (Knowles and Jakobiec). Occasional cells contain multiple, intracytoplasmic, rod-like structures referred to as myosin crystals (arrows). The whorled effect of haphazardly arranged myofibrils can be appreciated at this magnification (trichrome, ×1,300).

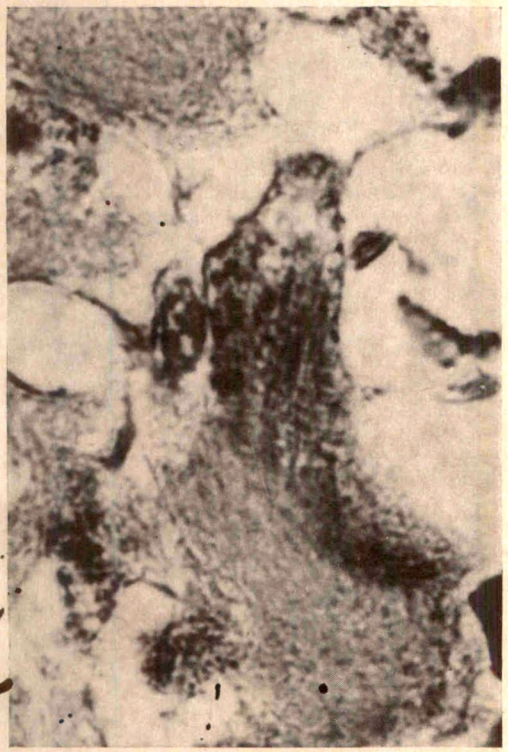


Fig. 9 (Knowles and Jakobiec). Diligent searching revealed the presence of cross striations (trichrome, ×1,500).

Summary

To our knowledge, this is the first fully documented case of an adult-type orbital rhabdomyoma in an 8-year-old white boy, which originated in the belly of the medial rectus muscle and grew into the anterior orbit to incorporate the trochlea. Incomplete excision resulted in recurrence; the lesion was misinterpreted as a rhabdomyosarcoma, and exenteration was performed. The patient was free of disease 25 years later. Reexamination of the original pathologic material showed the typical histology of an adult-type rhabdomyoma.

Adult-type rhabdomyoma, the most differentiated tumor in a spectrum of benign and malignant striated muscle neoplasms, should be distinguished from fetal rhabdomyoma (also benign) and pleomorphic rhabdomyosarcoma, the malignant striated muscle tumor most likely to be confused with rhabdomyoma.

An awareness of the benign nature of rhabdomyoma (rhabdomyoma never evolves into a sarcoma) should prevent unnecessary radical surgery. The tumor can be adequately managed by a local excision that includes all the lobulations of tumor within a margin of normal tissue.

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SURGICAL REVISION OF THE UPPER EYELID FOLD

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The integrity and symmetry of the upper eyelid fold contribute to the normal appearance of the eye. Any abnormality of the eyelid fold constitutes a cosmetic blemish. A variety of situations may result in eyelid fold deformities, but this problem is most commonly encountered as a complication of blepharoptosis surgery. An acceptable eyelid level may be marred by eyelid fold abnormalities or lash blepharoptosis (Fig. 1). Surgical revision of eyelid fold abnormalities may be necessary to achieve a completely satisfactory appearance of the upper eyelid.

The eyelid fold results from the insertion of fibers from the aponeurosis of the levator palpebrae superioris (LPS) muscle into the skin. This insertion exerts an upward and posterior traction on the skin. The skin above the insertion is under no tension and, therefore, hangs down forming an eyelid fold. If the levator muscle is paretic, it will exert less traction on the upper eyelid skin and result in an absent or diminished eyelid fold. An abnormal eyelid fold results from disruption of the normal levator muscle-skin relationship. By comparison, the levator muscle in the Oriental eyelid may not insert on the skin, or only on the skin near the eyelid margin. The scarcity of cutaneous insertions may result in the absence of the eyelid fold. The more anterior insertion of the orbital septum on the LPS aponeurosis permits a downward displacement of postseptal fat that further obscures an eyelid fold. In either case, surgical revision of the upper eyelid fold creates an adhesion of the levator muscle and tarsus to the skin to simulate the effect of the normal levator muscle insertion into the skin.

Most eyelid fold techniques have been described for revision of the Oriental eyelid.[1–8] Beard,[9] de Blaskovics,[10,11] Smith and Gunderson,[12] and Putterman and Urist[13] have described situations in which an eyelid fold procedure is used in the occidental eyelid. Holz[14] described an operation for entropion and trichiasis in 1879 that is similar to some eyelid fold procedures. Our technique has been applied primarily for the correction of eyelid fold abnormalities after blepharoptosis surgery. There are small variations in the technique, depending on the type of blepharoptosis operation that resulted in the abnormal eyelid fold.

METHOD

Anesthesia may be local or general. Even in general anesthesia, a subcutaneous injection of 1% lidocaine (Xylocaine) with 1:100,000 epinephrine is used to minimize bleeding. The incision was made at the site of the proposed eyelid fold. An ellipse of skin (Fig. 2, A), with the lower margin along the proposed eyelid fold, was excised in cases involving the Fasanella or frontalis suspension procedures or in Oriental eyelid revisions. Lash blepharoptosis may be corrected by excising the skin closer to the eyelid margin so the closure will rotate the lash follicles upward.

The skin was undermined to the eyelid

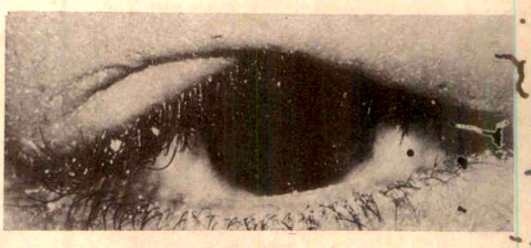


Fig. 1 (Cies and Baylis). Severe eyelid fold abnormality with lash blepharoptosis.

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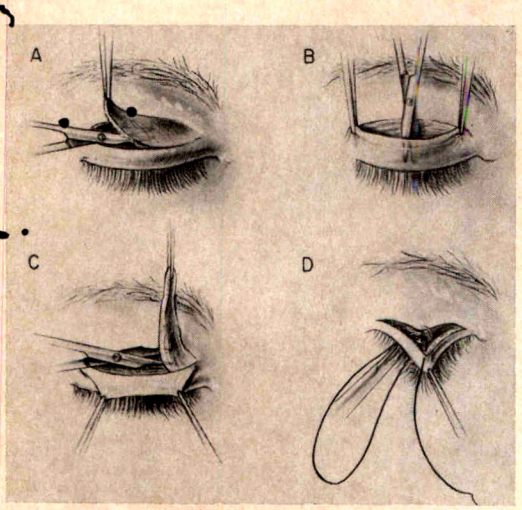


Fig. 2 (Cies and Baylis). A, Skin excision; B, Undermining of skin to eyelid margin; C, Excision of pretarsal orbicularis and oculi muscles; D, Full-thickness vertical mattress sutures.

margin, exposing pretarsal orbicularis oculi muscle and the LPS aponeurosis (Fig. 2, B). The anterior surface of the tarsus was exposed by excising all pretarsal tissue (Fig. 2, C); in patients who had a previous anterior levator muscle resection, this was usually unnecessary. In Oriental eyelids, the orbital septum was incised and excess fat was excised, if thinning of the eyelid was desired.

In frontalis suspension cases, the sling was usually at the upper edge of the tarsus and was avoided. If additional blepharoptosis correction was desired, we advanced the sling on the tarsus.

Three vertical mattress sutures (6-0 Dexon or silk) were introduced from the upper cul-de-sac through the conjunctiva above the tarsus, with one arm emerging through the LPS aponeurosis and out the upper edge of the skin incision. The lower arm came out the lower edge of the skin incision (Fig. 2, D). When the sutures were tied firmly, they caused an upward and posterior traction on the skin (Fig. 3). They were removed in five to seven days.

For two years, we performed surgery on 107 patients who had primarily blepharoptosis and eyelid fold abnormalities. Eighty-

TABLE 1

PROCEDURES FOR 89 CASES

	No. of Cases
Anterior levator muscle resections with eyelid fold sutures	43
Eyelid fold revision	(1)
Fasanella procedures	38
With eyelid fold technique	(24)
Without eyelid fold technique	(14)
Eyelid fold revision	(2)
Frontalis suspension procedures	8
Eyelid fold revision	(4)

nine patients had primary blepharoptosis procedures, including 43 anterior levator muscle resections with eyelid fold sutures, 38 Fasanella procedures (24 with the eyelid fold technique, 14 without), and eight frontalis suspensions (Table 1). Additionally, there were 18 eyelid fold procedures, including five after Fasanella procedures (two from our larger blepharoptosis series), five after anterior resections (one from the series), four after frontalis suspensions (all from the series), two associated with congenital anophthalmia, and one each from trauma and Oriental eyelid fold revision (Table 2).

CASE REPORTS

Case 1—This 13-year-old girl had a prior anterior levator muscle resection (but no eyelid fold sutures) performed on the right upper eyelid (Fig.

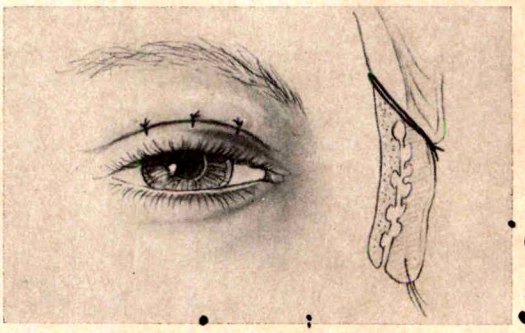


Fig. 3 (Cies and Baylis). Left, Sutures tied firmly with distinct fold and upward lash rotation. Right, Cross-section view showing suture origin above the tarsus, pulling skin edges posteriorly and vertically.

TABLE 2

PROCEDURES FOR 18 EYELID FOLDS

	No. of Cases
Fasanella procedure	5
Anterior levator muscle resection	5
Frontalis suspension	4
Congenital anophthalmos	2
Posttraumatic	1
Oriental	1

4, top). The eyelid level was good, but there was a poor, hooded eyelid fold with mild lateral lash blepharoptosis. An eyelid fold revision on April 4, 1971 resulted in an excellent eyelid fold (Fig. 4, bottom).

Case 2—This 16-year-old girl had severe congenital blepharoptosis of the left upper eyelid (Fig. 5, top). An anterior levator muscle resection was performed with eyelid fold sutures on April 15, 1971.

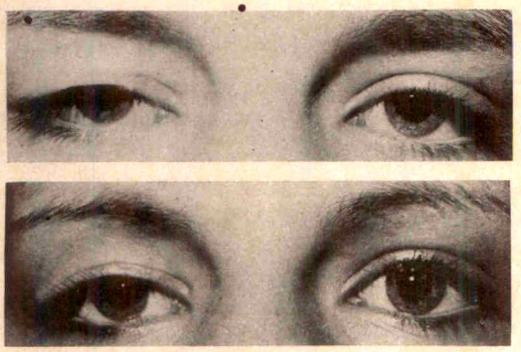


Fig. 4 (Cies and Baylis). Case 1. Top, After anterior levator muscle resection. A poor eyelid fold is present with redundant skin on each side of the fold. Bottom, 2.5 months after eyelid fold revision with definite eyelid fold.

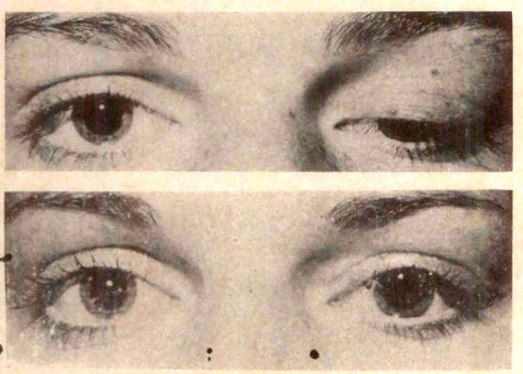


Fig. 5 (Cies and Baylis). Case 2. Top, Preoperative blepharoptosis, faint eyelid fold, and lash blepharoptosis. Bottom, Five months after anterior levator muscle resection and eyelid fold technique.

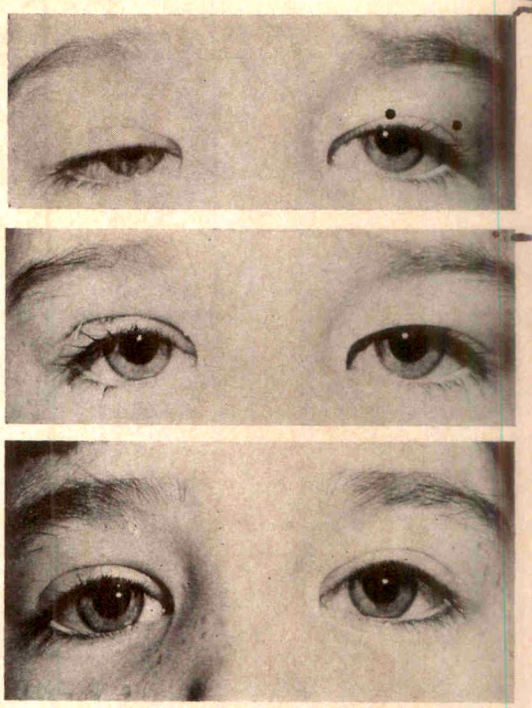


Fig. 6 (Cies and Baylis). Case 3. Top, Preoperative severe blepharoptosis in the right eye and mild blepharoptosis in the left eye. Center, Three weeks after Fasanella procedure on left upper eyelid and anterior resection on right upper eyelid. Symmetric eyelid levels marred by abnormal eyelid fold in left upper eyelid. Bottom, Left upper eyelid, 1.5 years after eyelid fold revision.

The result was an excellent eyelid level, eyelid fold, and lash rotation (Fig. 5, bottom).

Case 3—This 4-year-old girl had severe blepharoptosis in her right upper eyelid, with mild blepharoptosis in her left upper eyelid (Fig. 6, top). An anterior levator muscle procedure with eyelid fold sutures was performed on the right eyelid, and a Fasanella procedure without eyelid fold sutures on the left on Aug. 27, 1973. Symmetrical eyelid levels were marred by the poor eyelid fold in the left eyelid (Fig. 6, center). The revision of the left eyelid fold on Oct. 1 symmetrized the results (Fig. 6, bottom).

Case 4—This 8-year-old boy had mild blepharoptosis of the right upper eyelid (Fig. 7, top). A Fasanella procedure on Aug. 9 resulted in good eyelid levels, but an absent eyelid fold and poor lash rotation (Fig. 7, center). The eyelid fold procedure on Oct. 18 corrected these problems (Fig. 7, bottom).

Case 5—This 5-year-old girl had a fascia lata suspension procedure after a levator muscle tenotomy on Feb. 28, 1974 for right upper eyelid blepharoptosis associated with jaw winking. The absent eyelid fold and redundant skin obscured the raised

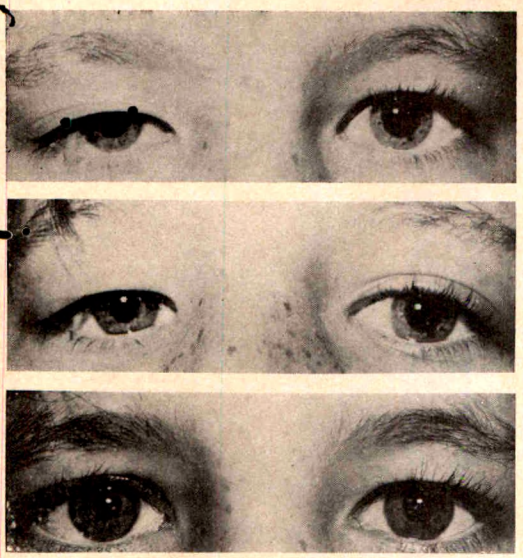


Fig. 7 (Cies and Baylis). Case 4. Top, Preoperative blepharoptosis, right upper eyelid. Center, Postoperative Fasanella procedure with poor eyelid fold and lash blepharoptosis. Bottom, 2.5 months after eyelid fold revision.

eyelid margin (Fig. 8, top). An eyelid fold procedure and an advancement of the previously placed sling on the tarsus resulted in an additional blepharoptosis correction and the eyelid fold (Fig. 8, bottom).

Discussion

In addition to the proper eyelid level, a normal upper eyelid should have a distinct symmetrical fold. The distal eyelid should be thin with no redundant skin, and no lash blepharoptosis should be present. In the normal eyelid, the LPS aponeurosis insertions accomplish this; to correct an abnormal eyelid fold, a procedure must produce a union of tarsus and levator muscle to the skin to simulate the normal levator function.

Several steps of the procedure contribute to producing the eyelid fold. The skin excision diminishes redundant baggy skin and aids in lash rotation. The degree of lash rotation depends on the amount of skin excised and the proximity of the lower margin of the incision to the lashes. The remaining distal skin is undermined to facilitate its displacement upward by the sutures and to permit new adhesions between the skin and deeper structures. Generally, it is difficult to obliterate fully the abnormal adhesions between the skin and levator muscle in patients with distorted or abnormally located eyelid folds. Excision of pretarsal orbicularis oculi muscle results in a thinner eyelid and permits adhesions between the skin and tarsus. The sutures attach the skin edges to the levator muscle, and this adhesion causes upward and posterior traction of the skin by the levator muscle. We found that a simple suture placed anteriorly through skin and levator muscle, as described in several eyelid fold techniques,[1-3,6,7,10] often resulted in a less distinct eyelid fold than those obtained from the full-thickness vertical mattress sutures.

In congenital blepharoptosis, the eyelid fold is frequently diminished or absent. The eyelid fold is usually produced or accentuated as part of most anterior levator muscle resections. Levator surgery that does not reconstitute the insertion of the levator muscle into the skin may result in an abnormal eyelid fold (Case 1). Therefore, we routinely finish an anterior resection with eyelid fold sutures to insure a distinct fold (Cases 2 and 3).

The Fasanella procedure resulted occasionally in an absent or a diminished eyelid fold and lash blepharoptosis. The eye-

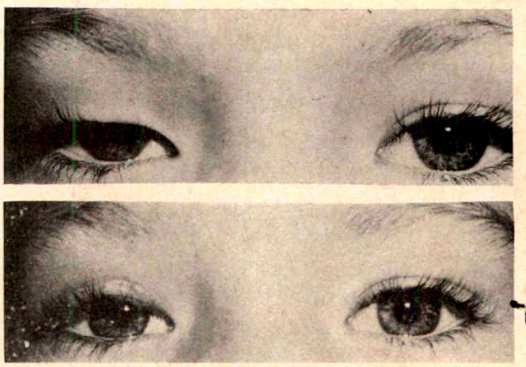


Fig. 8 (Cies and Baylis). Case 5. Top, Postoperative frontalis suspension in right upper eyelid. The eyelid fold is absent. Bottom, Three months after eyelid fold revision and advancement of the frontalis sling showing eyelid fold, elimination of redundant skin, and elevation of eyelid margin.

lid margin was elevated without shortening the levator muscle or excising the skin; occasionally, a relative laxity of the levator muscle pull on the skin and excess skin resulted in a diminished eyelid fold. Case 3 provides a comparison between the results of an anterior levator muscle resection with eyelid fold sutures and a Fasanella procedure without the eyelid fold procedure. In Case 4, a Fasanella procedure resulted in a good eyelid level but an abnormal eyelid fold and lash blepharoptosis. Beard[9] recently used an eyelid fold procedure after a Fasanella procedure to insure a good eyelid fold in senile blepharoptosis cases. We used the eyelid fold procedure routinely as part of the Fasanella operation.

Frontalis suspension operations generally alter the eyelid fold. Postoperatively, there is often a poor or absent eyelid fold (Case 5). Occasionally, there may be redundant skin hanging over the eyelid margin to give the illusion of a lowering of the eyelid margin (Case 5). In unilateral cases, eyelid fold revision produces an eyelid fold and may result in an apparent elevation of the eyelid margin. The symmetry of bilateral cases may preclude eyelid fold revision, unless there are obvious eyelid fold abnormalities. The sling may be advanced on the tarsus during the eyelid fold revision to revise slight undercorrections of the blepharoptosis (Case 5).

Occasionally, an eyelid fold abnormality is the result of trauma or surgical exploration. The absence of an eyelid fold in an Oriental results, basically, from the lack of levator muscle insertions into the skin. In both situations, the eyelid fold procedure may be used to form or reconstitute an eyelid fold.

Finally, an absent eyelid fold often accompanies the deformities of congenital anophthalmia, and the eyelid fold procedure may be used in the overall cosmetic reconstructive efforts.

Summary

We performed surgery on 107 patients primarily with blepharoptosis and eyelid fold abnormalities, between 1973 and 1974. Production of an eyelid fold at the time of an initial blepharoptosis procedure should be a primary goal. Lack of a distinct symmetrical upper eyelid fold constituted a cosmetic blemish and necessitated revision.

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RHABDOMYOSARCOMA OF THE ORBIT IN THE NEWBORN

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Rhabdomyosarcomas are usually malignant tumors, and the most common, primary malignant orbital tumor in children.[1] We found, however, only five such cases reported in newborns.[1,3–6] We studied a rhabdomyosarcoma of the orbit in a full-term newborn infant. The mass was located at the midline on the floor of the orbit, was cystic in nature, and extended through the lacrimal fossa into the nasal cavity.

Histologically, rhabdomyosarcomas are pleomorphic and the cells may be anaplastic.[2] Spindle cells with eosinophilic cytoplasmic fibrils that are usually cross-striated are used to identify the tumor, but the diagnosis is sometimes difficult,[2,3] especially if the biopsy specimen is small.[4] Striations can be demonstrated after a careful search in 60% of the specimens. Most rhabdomyosarcoma specimens vary widely in histology from area to area and, hence, pose difficulty in grading.[1,7]

CASE REPORT

A full-term black male infant was born spontaneously and without complications at the Jewish Hospital and Medical Center of Brooklyn. He was a second child, weighed 3,304 g (7 lb 6 oz), and his APGAR score was 9. A 2- to 3-cm, round bluish mass was noted centrally located on the right lower eyelid. During the first ten days, the baby exhibited typical neonatal hyperbilirubinemia that resolved rapidly without complications.

On the third day, the eyelid mass was 3 cm in diameter, firm, and bluish, with a centrally raised white area, and seemed cystic in consistency. Ultrasonography confirmed a cystic mass. We aspirated 2 to 3 ml of a chocolate-colored liquid that contained many red blood cells but no crystals, bacteria, or fungi. A right orbital venogram showed that the right superior ophthalmic vein was displaced medially and cephaladically. The radiologic impression located the mass anteriorly in the orbit, depressing the orbital floor. The globe was displaced superiorly and medially. Injection of radiopaque material revealed an intact cystic wall that did not appear to communicate with any other cavities, nor was any vasculature noted.

The mass was partially excised on the 12th day. It was beneath the periosteum and had penetrated inferonasally through the lacrimal bone into the nasal cavity.

Microscopically, the tumor was composed of small, rounded cells. No cellular striations were found in the initial specimen although occasional oval cells were seen. The cells had poorly defined borders and were either grouped in large, dense masses or in small clusters enmeshed in fibrovascular tissue. One area exhibited a ring-shaped group of rounded cells that we thought was representative either of a rosette differentiation or an alveolar type of structure (Fig. 1). A typical section of the tumor is represented (Figs. 2 and 3). Two independent pathology reports indicated neuroblastoma; a third report, however, indicated "embryonal sarcoma, probable embryonal rhabdomyosarcoma."

After surgery a metastatic survey was negative. Analysis of a 24-hour urine collection for VMA, HMA, and catecholamines was negative. The physical examination showed that systolic blood pressure results varied from 110 mm Hg to 180 mm Hg on different days. Results of bone marrow aspirations were negative. Due to the size of the mass, the right fundus could not be examined preoperatively. The left fundus was entirely normal. Postoperatively, the right eye was also normal.

At 1 month of age, the patient's right eye began to evidence proptosis and one week later, a small anterior cervical node was noted on the right side. This was excised and the pathology report indicated a neuroblastoma.

At 6 weeks of age, the infant received 100 mg of intravenous cyclophosphamide and 0.5 mg of intravenous vincristine sulfate, once weekly for a total of four doses each. The proptosis, however, progressed severely; at 7 weeks of age, radiation therapy to the right orbit, 200 rads per day for six days, was begun. At 8 weeks of age, the proptosis started to recede and corneal opacifications appeared. At 13 weeks of age, an incomplete exenteration was supplemented with local cryotherapy of the remaining tissue but processing was inadequate. Cervical adenopathy persisted and shortly afterwards, another skeletal survey revealed metastasis to the right tibia.

The child was subsequently transferred to the Memorial Hospital for Cancer and Allied Diseases where he died. The postmortem diagnosis was fetastasic rhabdomyosarcoma.

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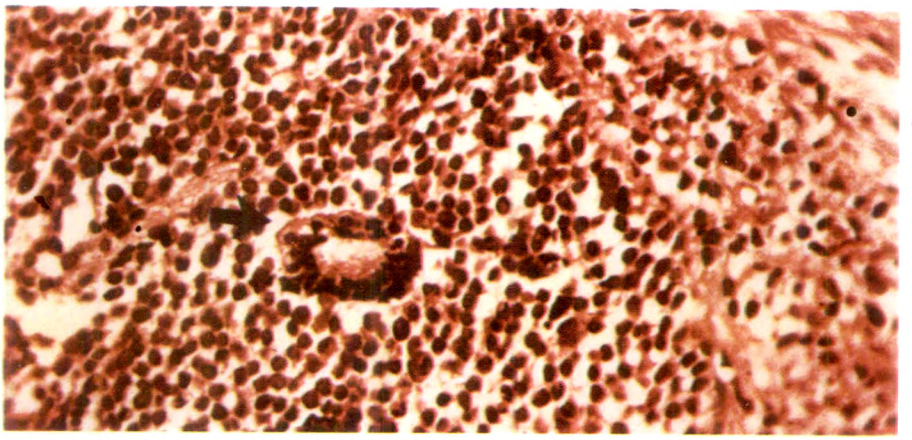


Fig. 1 (Ellenbogen and Lasky). Tumore cells with ill-defined borders and fibrovascular tissue. An arrow points to the area of rounded cells forming a ring-like structure (hematoxylin and eosin, x 400).

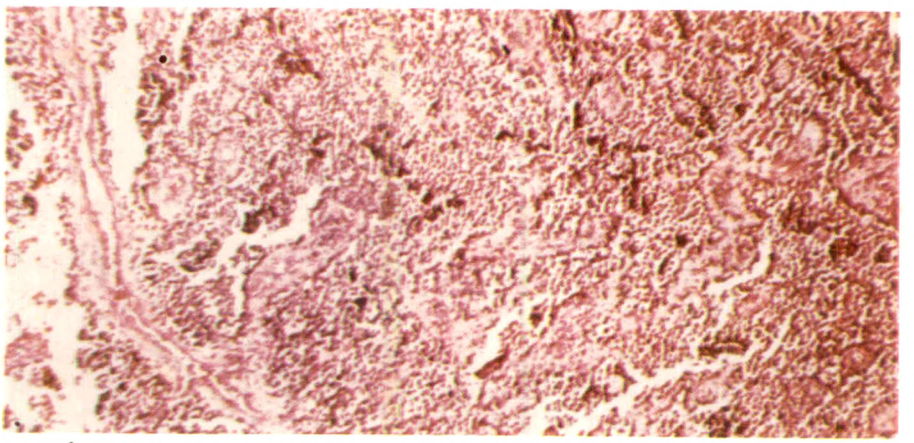


Fig. 2 (Ellenbogen and Lasky). Tumor wall demonstrating oval or elongated cells, some with eosinophilic cytoplasm (hematoxylin and eosin, x100).

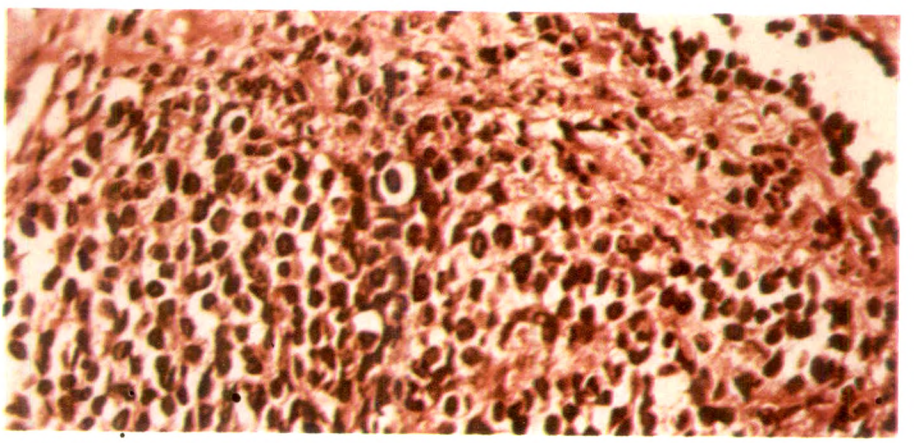


Fig. 3 (Ellenbogen and Lasky). Higher magnification of an area of the cust wall (hematoxylin and eosin x400).

Discussion

As we have noted, it is unusual to find this condition in the newborn.[1,3-6] This case is also unusual due to the tumor's cystic nature and its extension via the lacrimal fossa into the nasal cavity. Microscopically, the tumor was composed of primitive cells. No striations were apparent in the first two specimens. The ring-shaped cell group (Fig. 1) and the fluctuation in the arterial blood pressure probably were responsible for the initial diagnosis of neuroblastoma, although the urine studies for VMA and HMA were negative. The final diagnosis of rhabdomyosarcoma was established microscopically at autopsy.

Summary

A full-term black boy had a 2- to 3-cm, round, bluish mass on his right lower eyelid at birth, later diagnosed as rhabdomyosarcoma. It was cystic in nature and extended into the nasal cavity. The tumor was initially classified as neuroblastoma. The child died eight months later and the necropsy report confirmed an original ophthalmologic pathology diagnosis of embryonal rhabdomyosarcoma.

Acknowledgments

We thank Robert D. Reinecke, M.D., and Kurt Simmons for their editorial assistance.

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LEIOMYOMA AND LEIOMYOSARCOMA OF THE ORBIT

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While leiomyoma of the orbit, a benign tumor of smooth muscle, has been the subject of sporadic articles,[1-4] orbital leiomyosarcoma, its malignant counterpart, has not been described in the English literature.[5] We compared two orbital leiomyomas and two orbital leiomyosarcomas with regard to their clinical behavior and histopathologic features. Leiomyosarcoma proved to be a highly malignant metastasizing orbital sarcoma of adults. A case of embryonal rhabdomyosarcoma of the orbit that was diagnosed as a leiomyosarcoma by light microscopy, but shown to be a rhabdomyosarcoma by electron microscopy, is also included in this study to highlight the clinical, pathologic, and histogenetic differences between these two classes of muscle tumor.

CASE REPORTS

Leiomyomas—CASE 1—A 17-year-old white boy who was known to have congenital megacolon developed a mass under the skin of the right medial canthal area that had gradually enlarged during a two-month period. There was no proptosis, no diplopia, no inflammation or tenderness, and no epiphora. Uncorrected visual acuity was 20/20 in each eye and examination of the globes was unremarkable. The x-ray studies of both orbits were interpreted as normal, and visual fields were full.

Four weeks after he was first examined, the tumor was removed under general anesthesia. A 3-cm vertical incision was made 10 mm nasal to the inner canthus of the right eye, exposing a firm, nodular encapsulated subcutaneous mass, about 10 × 15 mm and about 5 mm in thickness; the mass was adherent to the periosteum of the medial orbital rim and partially enveloped the upper pole of the lacrimal sac.

The patient has been followed carefully for 16 years; there has not been a recurrence of the mass, nor has there been any ocular complaint.

CASE 2—A 34-year-old white woman with a history of recurrent left sinusitis for two years began to notice proptosis of the left eye associated with diplopia (Fig. 1).

Examination of the eyes showed 6 mm of proptosis of the left eye (Fig. 1). There was swelling of the left upper eyelid with 2 mm of blepharoptosis. The corrected visual acuity was R.E.: 20/30, and L.E.: 20/40. Pupils were reactive, but ductions of the left globe were limited in elevation and abduction. The optic disk showed slight papilledema. Visual fields were full. No discrete mass could be palpated, and general physical examination was unremarkable. The x-ray studies showed an increased soft tissue density within the left orbit and enlargement of the superior orbital fissure.

At the time of surgery in 1935, a large lateral canthotomy was performed, and an encapsulated mass was located in the muscle cone near the apex of the orbit lying between the lateral rectus muscle and the optic nerve (Fig. 2). The tumor was freed by blunt finger dissection, except at the superior orbital fissure, where it was adherent; in this area the tumor had to be severed by sharp dissection with a tonsil snare.

Postoperatively, the globe remained fixed in external rotation. Two millimeters of proptosis persisted, and the blepharoptosis of the left upper eyelid increased to 5 mm. The following year an operation on the left horizontal rectus muscle was performed to correct 40 diopters of left exotropia. Corrected visual acuity was 20/30 in each eye.

The patient did not return for further examination until seven years later, when she reported that the proptosis of the left eye had begun to increase. Visual acuity at that time was R.E.: 20/30, and L.E.: 20/70. The left eyelids were edematous, and the conjunctiva was chemotic. Vertical striae were seen in the left fundus involving the macula. A mass was palpated along the upper and nasal portion of the left orbital margin. An exenteration was advised, but the patient refused further surgery. She was then treated in 1943 with 11,400 roentgens in divided doses to the left orbital region. The proptosis of 3 mm gradually evolved to an enophthalmos of 2 mm. presumably from regression of the tumor mass and fibrosis of orbital connective tissue following radiotherapy. During a five-year period of observation, there was no further recurrence of the tumor; the patient developed postradiation keratinization of the cornea, trichiasis, and an indolent corneal ulcer.

A year later, the orbital tumor recurred and the orbit was exenterated. She then was admitted to

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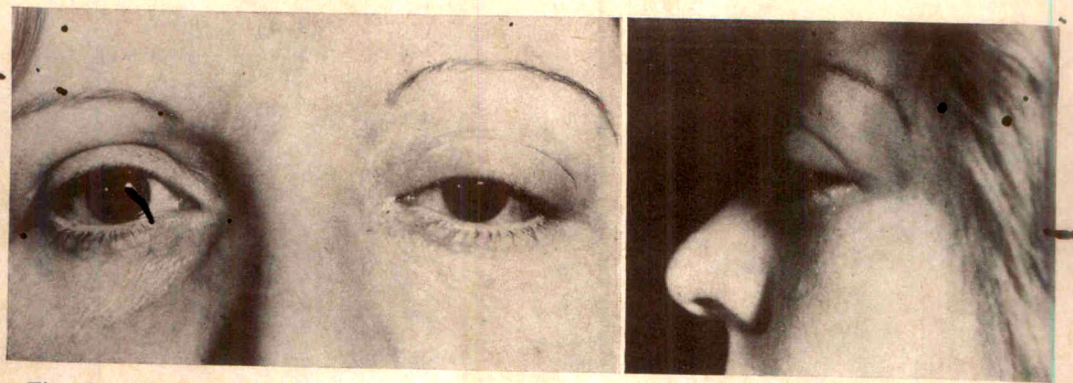


Fig. 1 (Jakobiec and associates). Case 2. Thirty-four-year-old woman had a superior orbital leiomyoma that extended through the superior orbital fissure. Note the fullness of the left upper eyelid and the relative effacement of the eyelid fold.

another hospital because of central nervous system symptoms, and at the time of craniotomy residual sarcoma was partially excised from the region of the left sphenoid bone. Two years after that, she was again admitted to a hospital, where biopsy of a scalp nodule revealed metastatic sarcoma; x-ray films of the spine revealed probable metastatic lesions to the lumbar spine.

A year later, in 1952, at the age of 51, she became bedridden, anorexic, anemic, paraplegic, dropsical, decubital, and died.

The final diagnosis was leiomyoma of the orbit with intracranial extension, recurrent, followed by radiation-induced sarcoma.

Leiomyosarcomas—CASE 3—A 58-year-old white woman in good general health complained of a blur in the temporal field of her right eye, first noted 15 months previously.

Visual acuity was R.E.: 20/40, and L.E.: 20/20. The right eye was proptosed 3 mm and deviated 1 mm laterally. Extraocular motions of the right eye were restricted in all directions. The episcleral vessels on the nasal aspect of the right globe were noticeably dilated (Fig. 3). No mass was palpable. The right disk was edematous; the vessels in the posterior pole were engorged; a macular star figure was present, and there were choroidal striae near the disk. The x-ray studies showed a symmetrical enlargement of the right orbit of 1 mm. The left eye was unremarkable.

At the time of the Krönlein operation a mass was palpated in the nasal part of the muscle cone; an auxiliary incision was made in the conjunctiva nasally, exposing a mass about 1 x 2 cm, lying nasally between the medial rectus muscle and the globe, extending posteriorly toward the apex of the orbit. It was excised, and appeared to be nonencapsulated, gray, and friable.

At follow-up examination one year after surgery, there was no evidence for a local recurrence of the neoplasm. However, the patient died 15 months after the Krönlein orbitotomy of metastatic disease. She also had had a removal of an ovarian carcinoma six years before the Krönlein operation. However, a biopsy of the right lower rib cage just before death was read as "metastatic sarcoma" rather than metastatic ovarian carcinoma.

CASE 4—A 59-year-old white woman complained



Fig. 2 (Jakobiec and associates). Case 2. The main tumor mass was encapsulated (left), but the capsule was broken and the tumor transected where it extended through the superior orbital fissure (right).



Fig. 3 (Jakobiec and associates). Case 3. Fifty-eight-year-old woman with mild proptosis and dilatation of the nasal episcleral vessels. The patient had a leiomyosarcoma under the belly of the medial rectus muscle.

of proptosis of the left eye which had been present for 1½ years. Review of family photographs revealed that this had probably been present for four years. With the Hertel exophthalmometer 9 mm of proptosis of the left eye was measured.

The left eye could not be depressed, and there was slight limitation of motion temporally. Examination of both globes was unremarkable, visual fields were full, and corrected visual acuity was 20/20 in each eye.

A Krönlein orbitotomy was performed, and a firm bilobed, partially encapsulated mass was removed from the posterior part of the orbit, lying between the inferior and lateral rectus muscle. Postoperatively, the patient complained of diplopia. There was increased limitation of motion laterally, and the left pupil remained dilated.

Three years later the proptosis recurred, and an indentation of the globe was noted medially which resembled a choroidal tumor. A complete medical and gynecological appraisal of the patient, including x-ray studies of all the long bones, failed to reveal evidence either for metastasis or for any disturbance of her general health. A retro-ocular tumor was excised through a nasal incision in the conjunctiva. Nine months after this operation, 5 mm of proptosis of the left eye appeared, visual acuity dropped to 20/40, and a 1½-cm mass was delivered through a wide lateral canthotomy.

Two months after this operation, massive proptosis recurred, vision decreased to light perception, and the globe became immobile. An exenteration was performed.

On her fifth admission eight months later, a final surgical procedure was performed for recurrence of orbital tumor and the patient was referred for radiotherapy to her local hospital. The patient died exactly one year later of an undifferentiated sarcoma metastatic to the lung and brain, demonstrated at autopsy.

Comment—The two patients with leiomyomas of the orbit were both young. In one the tumor did not recur after a local excision during a 16-year period of observation. In the second, an encapsulated leiomyoma of the orbit was identified and excised through a wide lateral canthotomy; it was noted to extend into the anterior cranial fossa through the superior orbital fissure and was amputated with a tonsil snare. The tumor did not recur until seven years later, and was treated with radiotherapy after the patient elected not to have further surgery. This was in 1943 when guidelines for dosage were in a state of flux, and 11,400 roentgens were administered. Six years later, the tumor recurred a second time, and soon after had metastasized to the scalp and spine. Review of sections showed that the tumor, originally benign, had become malignant. It is a moot point whether the radiotherapy, which would be considered excessive by modern standards, caused malignant transformation of the original tumor, or induced another sarcoma.

In the other two patients, both older (in their sixth decade), a leiomyosarcoma involving the muscle cone caused proptosis as the initial sign. The tumors proved to be highly malignant. The first patient, who was treated by local excision, died of metastatic tumor 15 months after surgery. The second developed multiple local recurrences in the orbit, necessitating five orbitotomies, including an orbital exenteration; exactly one year after the fifth operation she died of metastatic disease to the lung and brain.

Rhabdomyosarcoma—CASE 5—A healthy 7-year-old white girl rapidly developed proptosis of the right eye measuring 2 mm within one week. Associated with the proptosis were blepharoptosis of the right upper eyelid, right hypertropia, and a palpable mass beneath the conjunctiva in the lower fornix measuring approximately 1½ × 1 cm.

Uncorrected visual acuity was R.E.: 20/40, and L.E.: 20/20. The palpebral fissure measured 4 mm on the right and 9 mm on the left. Pupils were reactive, but testing of the extraocular motions showed paresis of the right inferior rectus muscle. Ophthalmolmoscopy of the right fundus showed horizontal chorioretinal striae below the macula. The orbits were studied by routine x-ray examination and by tomography and were unremarkable. General physical examination by a pediatric consultant, including radiographic survey of the skull, thorax, spine, and hips, and including study of aspirated bone marrow, revealed no evidence for metastasis.

Biopsy specimens of the mass showed an undifferentiated spindle cell sarcoma, thought to be a leiomyosarcoma, a malignant schwannoma, or an embryonal rhabdomyosarcoma, in that order of preference. Difficulties attending precise histopathologic diagnosis revolved around the varied character of the sarcomatous cells.

The patient received radiotherapy in the amount of 6,000 rads administered by cobalt 60 in divided doses during a five-week interval; she has done well with no evidence for recurrence of the tumor during an examination period of one year.

RESULTS

Light microscopy—LEIOMYOMAS—The two benign tumors (Cases 1 and 2) showed

similar histologic features. Both tumors possessed distinct capsules (Figs. 2 and 4). Small encapsulated satellite lobules occassionally projected from the main tumor mass (Fig. 5). The tumor cells were organized into long fascicles (Figs. 4-6). With the reticulin stain, abundant reticulin fibers were demonstrated wrapping around individual cells and forming striking spiral configurations (Fig. 7). The nuclei were oval to cigar-shaped, with rounded ends; nuclear palisading was frequent. No mitoses were found. The trichrome stain revealed intense cytoplasmic fuchsinophilia; longitudinal nonstriated cytoplasmic filaments were clearly discerned with the oil immersion lens. On cross-section, many of the tumor cells showed perinuclear halos. Large areas of both tumors were replaced by dense collagen, reminiscent of keloid fibers.

Capillaries were conspicuously distributed throughout the tumors. Most of the vessels were bloodless, suggesting lymph channels or a lack of communication with the orbital circulation. When the tumor cells compressed the vessels into interconnecting slits, the appearance of a hemangiopericytoma was created (Fig. 8). Papillae of tumor cells sometimes pushed into the larger vascular space (Fig. 6).

LEIOMYOSARCOMAS—Case 3 displayed a striking, repeating arrangement of spherules of tumor cells onion-skinning around capillary-sized vessels (Figs. 9-11). At the periphery of the tumor, which was not encapsulated, units of tumor cells organized about a central capillary detached from the main mass (Fig. 9). The tumor invaded the orbital musculature. The cytoplasm stained deeply with the trichrome stain, and myofibrils were easily seen. There was one mitosis for every three high-power fields examined; occasionally three mitoses were found in a single field. The nuclei were irregularly shaped and hyperchromatic; multinucleated cells were scattered throughout the tumor (Fig. 11).

Case 4 had a less distinctive but equally pronounced vascular pattern created by ectatic, usually bloodless, spaces. These vessels were frequently invaded by tumor cells (Fig. 12). Nuclear palisading was not found, and the diagnosis rested on the demonstration of cytoplasmic filaments with the tri-

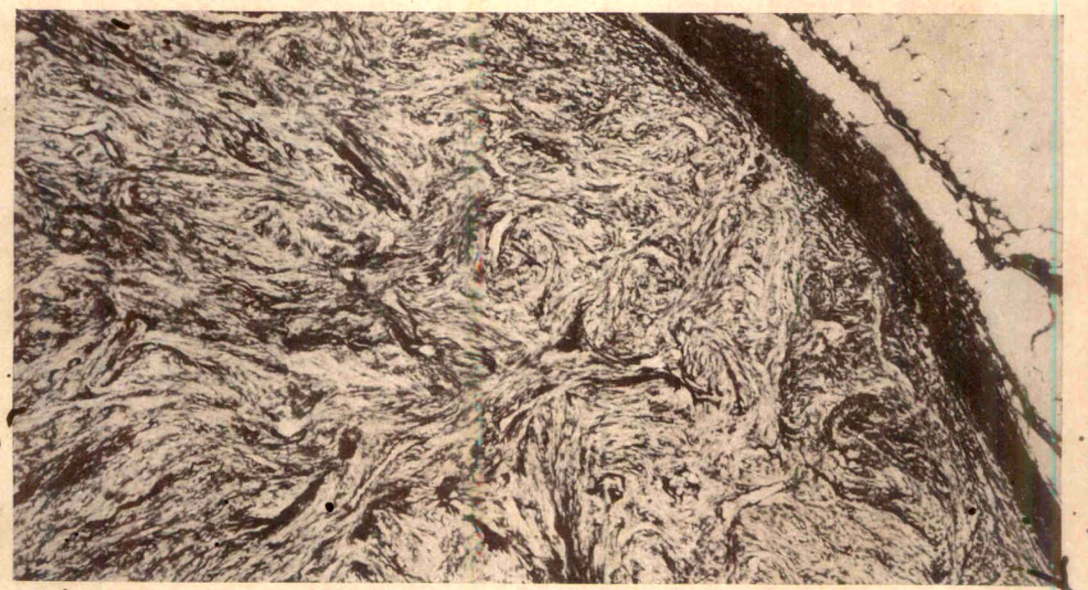


Fig. 4 (Jakobiec and associates). Leiomyoma composed of bundles of tumor cells. A thick capsule and the orbital fat are shown on the right (Laidlaw reticulum stain, ×80).

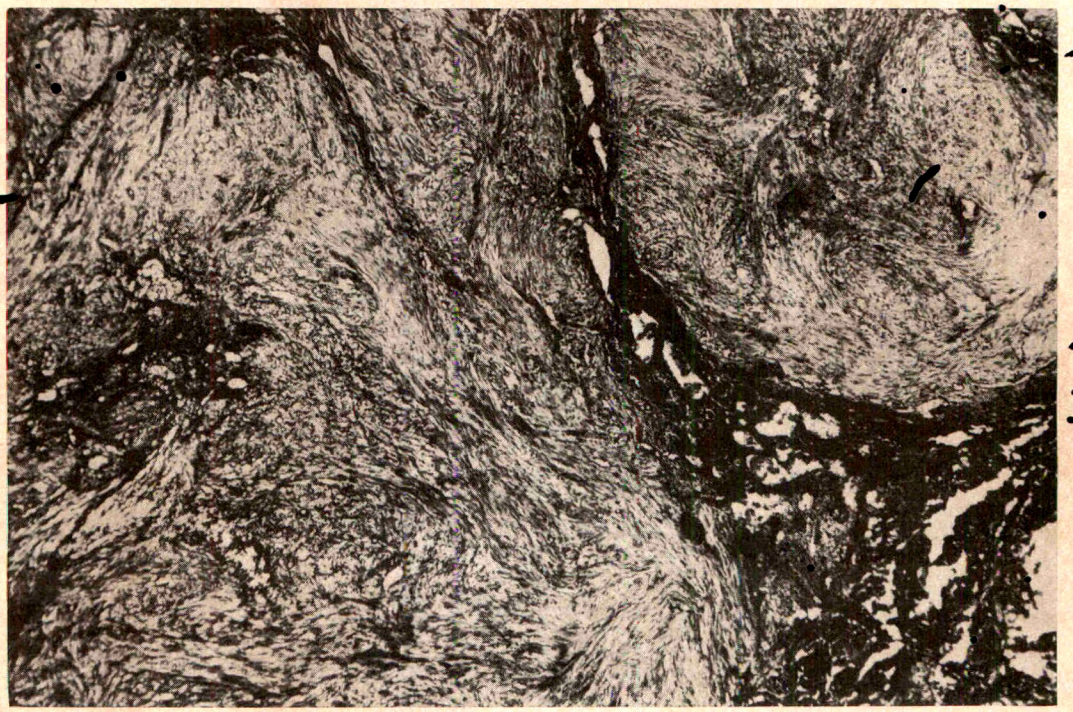


Fig. 5 (Jakobiec and associates). Small satellite nodule on right projects from the bulk of the leiomyoma on the left (Masson trichrome, ×80).

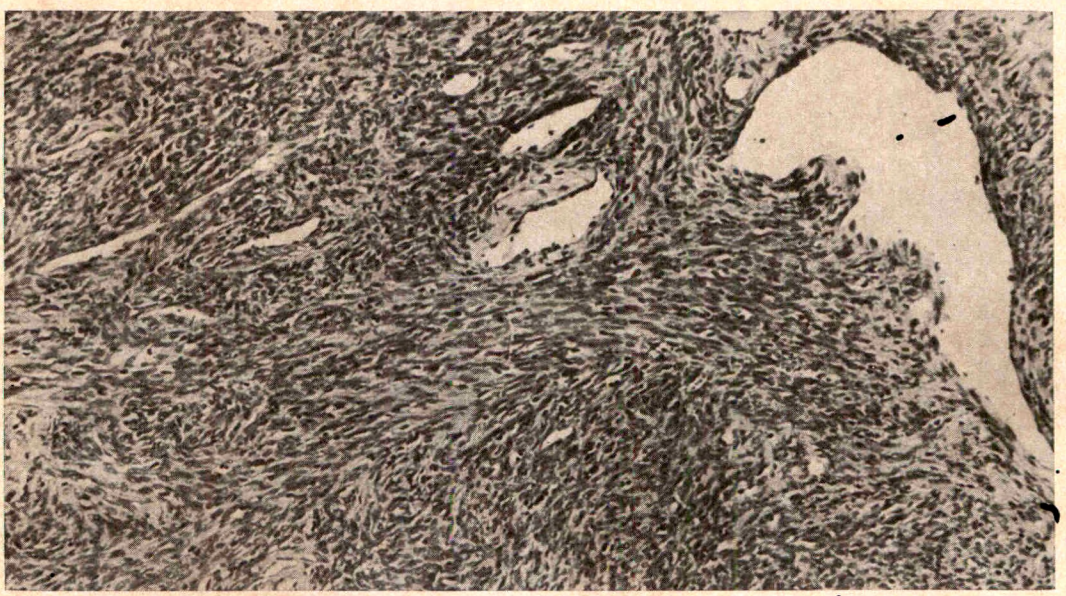


Fig. 6 (Jakobiec and associates). Leiomyoma. The tumor cells are arranged in bundles. Bloodless vascular spaces are prominent. Two papillae of benign tumor cells project into the large lumen on the right (hematoxylin and eosin, ×220).



Fig. 7 (Jakobiec and associates). Leiomyoma. Abundant reticulin fibers, often displaying a spiraling configuration, wrap around the tumor cells. The blood vessels are also clearly outlined (Laidlaw reticulum stain, ×180).

chrome stain. Mitoses were numerous in the first biopsy specimen (one mitosis per four high-power fields), and the number of mitoses increased with subsequent recurrences. On the last orbital biopsy, there were up to ten mitoses per high-power field.

The cytologic features became more outspokenly malignant during the recurrences.

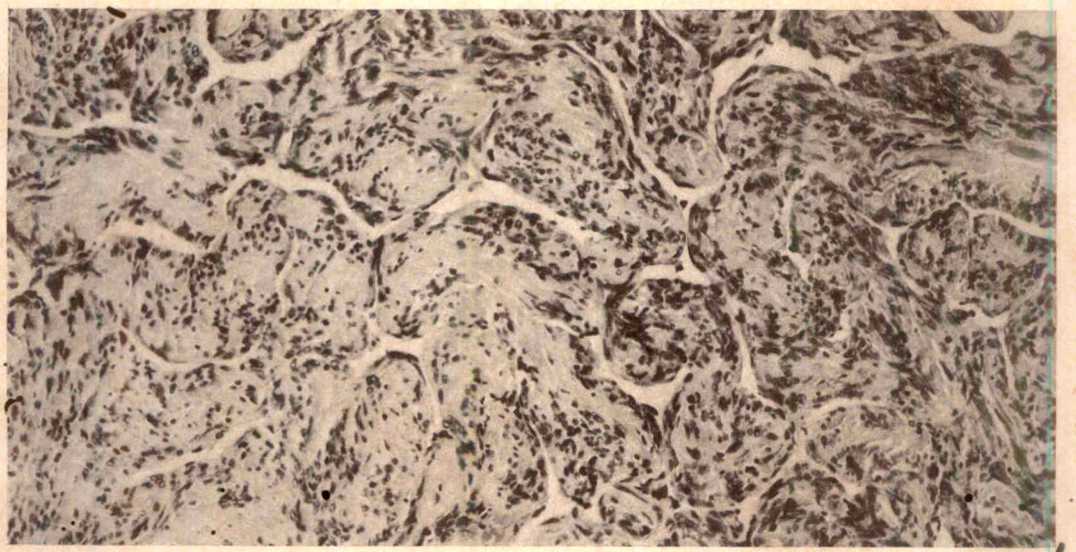


Fig. 8 (Jakobiec and associates). Leiomyoma. An elaborate plexus of slit-like vascular spaces. The nuclei have a tendency to palisade and there is moderate collagen deposition (hematoxylin and eosin, ×220).

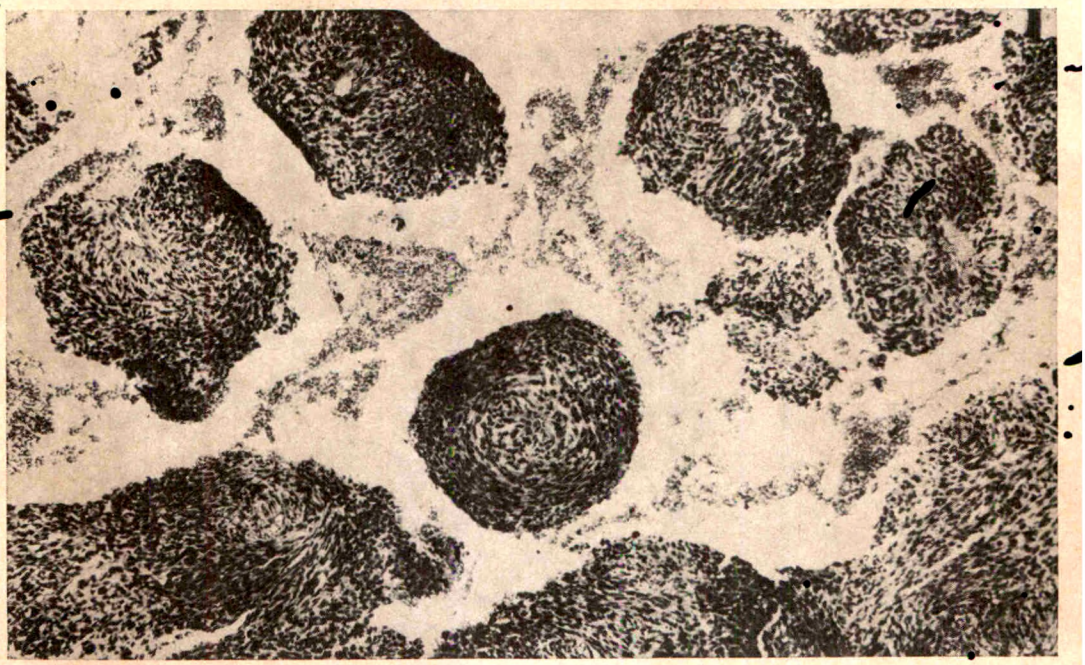


Fig. 9 (Jakobiec and associates). Case 3. Leiomyosarcoma. Spherules of tumor cells, each containing a central capillary, have detached from the main tumor mass below (hematoxylin and eosin, ×80).

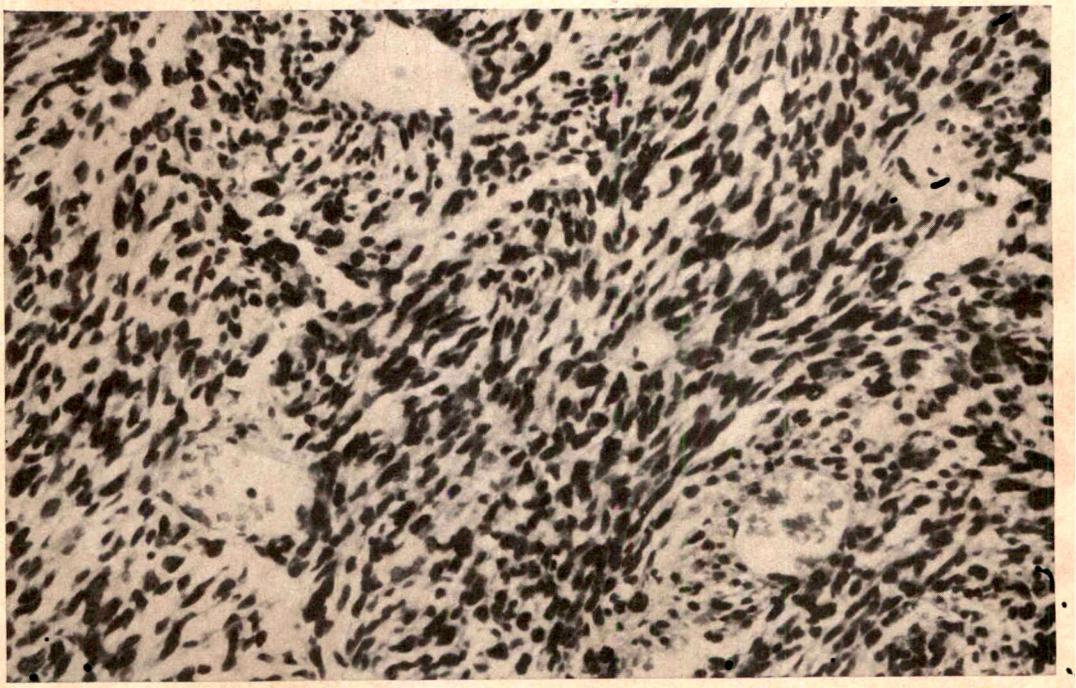


Fig. 10 (Jakobiec and associates). Case 3. Leiomyosarcoma. The orientation of the tumor cells around capillaries, with blending at the periphery of each unit, was maintained throughout the tumor (hematoxylin and eosin, ×280).

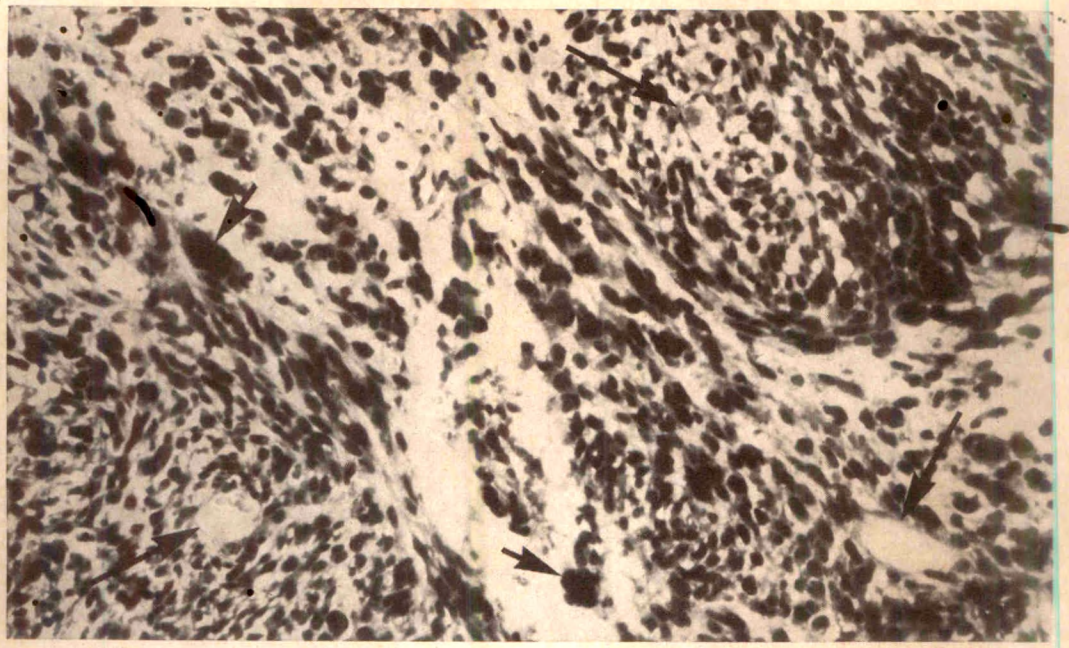


Fig. 11 (Jakobiec and associates). Case 3. Leiomyosarcoma. The long arrows point to central capillaries, and the short arrows point to multinucleated tumor cells (hematoxylin and eosin, ×280).

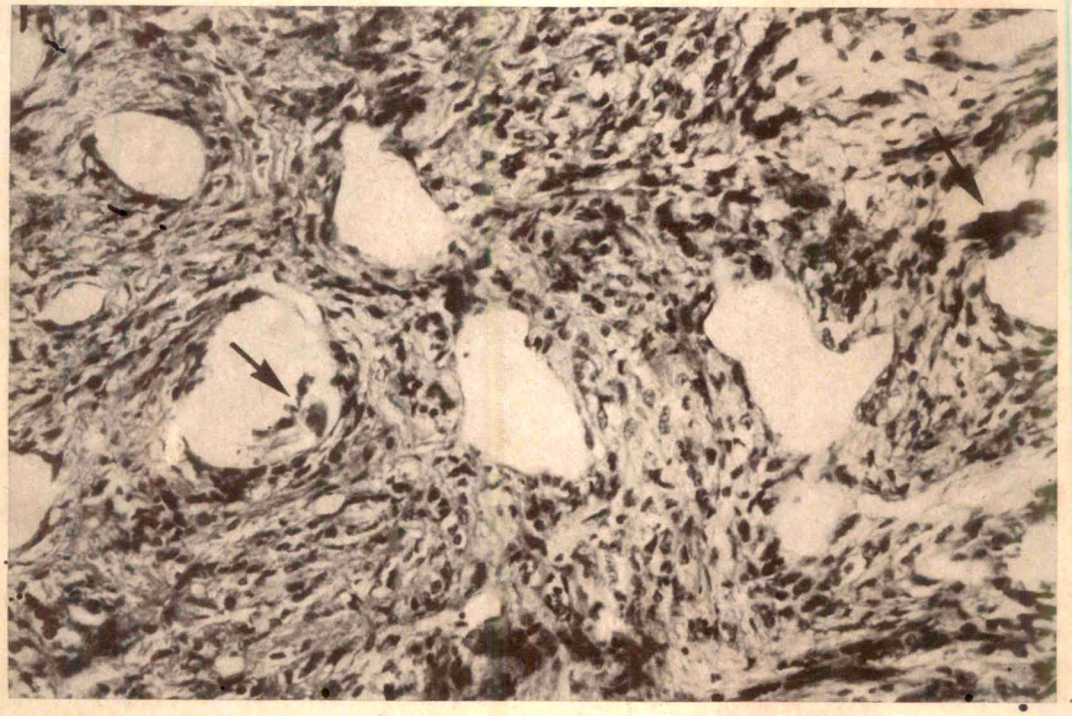


Fig. 12 (Jakobiec and associates). Case 4. Leiomyosarcoma. The tumor is perforated by ectatic vessels. The arrows indicate tumor cells in the lumina. The nuclei are hyperchromatic (hematoxylin and eosin, ×320).

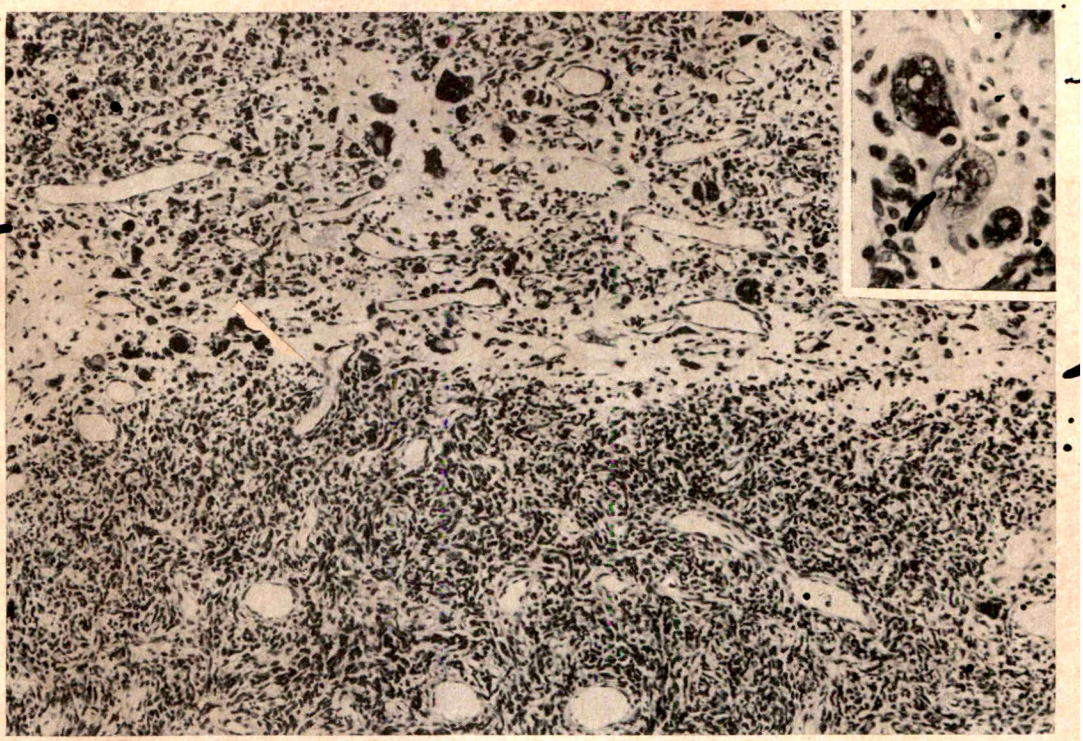


Fig. 13 (Jakobiec and associates). Case 4. Leiomyosarcoma. In a brain metastasis, looser (above) and more solid (below) areas occurred. Giant cells were conspicuous. Note the continued presence of a prominent vascular pattern (hematoxylin and eosin, ×120; inset ×320).

The nuclear-cytoplasmic ratio increased; at times the nuclei appeared almost naked. Giant cells were numerous. In the lung and brain metastases examined at autopsy (Fig. 13), the prominent vascularity of the initial tumor was well maintained, but the cells were much more pleomorphic, with bizarre tumor giant cells dominating the picture.

RHABDOMYOSARCOMA—The tumor was composed of elongated spindle cells arranged either in bundles or suspended in a looser myxomatous matrix. The cells had a distinct tendency to palisade (Fig. 14). There were two mitoses per high-power field. The tumor invaded the orbital fat and musculature and was not encapsulated. The trichrome stain disclosed deep cytoplasmic acidophilia but cross-striations or longitudinal fibrils were not detected.

Electron microscopy—The ultrastructure of a previously reported[4] leiomyoma of the orbit is shown. The tumor cells possessed copious cytoplasmic filaments with fusiform densities (Fig. 15, upper left). These filaments excluded other organelles, especially the rough-surfaced endoplasmic reticulum. The cell membrane possessed pinocytotic vesicles, plasmalemmal densities (grapple plaques), and basement membrane formation.

The rhabdomyosarcoma was composed of two types of cells. The rhabdomyoblasts were either elongated or ovoid cells and contained polyribosomes and a few short profiles of rough-surfaced endoplasmic reticulum. The Golgi apparatus was poorly developed. In many tumor cells there were thick filaments, sometimes arranged in a haphazard fashion (Fig. 15, lower left); rarely the filaments were arranged into abortive sarcomeres (Fig. 15, upper right).

An interrupted basement membrane enveloped the more differentiated rhabdomyoblasts.

A second population of fibrocytoid cells possessed well-developed rough-surfaced endoplasmic reticulum. These cells failed to form any basement membrane material. Immediately subjacent to the cell membrane of the fibrocytoid cells were sheaths of thin cytoplasmic filaments without fusiform densities (Fig. 15, lower right).

Thick filaments, even without sarcomeric organization, are not found in cells other than rhabdomyoblasts.[6-8] In the present rhabdomyosarcoma, the infrequently well arranged sarcomeres unequivocally established the diagnosis. The subplasmalemmal thin filaments in the fibrocytoid cells might initially incline one toward the diagnosis of a leiomyosarcoma, but the filaments were situated only in this location and did not display fusiform densities. Such filaments are composed of actin protein and are found in many cell types, subserving cell motility.[9] The fibrocytoid cells in rhabdomyosarcoma are probably neoplastic. In single cell tissue cultures of striated muscle, fibrocytoid cells grow out along with the rhabdomyoblasts, indicating that they are indeed kindred.[10]

Discussion

All of the tumors in the present series were classified in the Eye Pathology Laboratory at the Edward S. Harkness Eye Institute as leiomyosarcomas before they were critically reviewed (Table). On this basis, a case of orbital leiomyoma was reported earlier[4] and therefore not included in this study as the only example of leiomyoma of the orbit on file at the Eye Institute. Of the cases diagnosed as leiomyosarcoma, two have stood up to close histopathologic scrutiny, two have been reclassified as leiomyomas, and one has proved to be a rhabdomyosarcoma. The histopathological reevaluation was conducted independent of the determination of the clinical follow-ups; the two patients with diagnoses of leiomyomas had prolonged survivals, whereas the two patients having leiomyosarcomas died from their disease with distant metastases. The patient with rhabdomyosarcoma had a

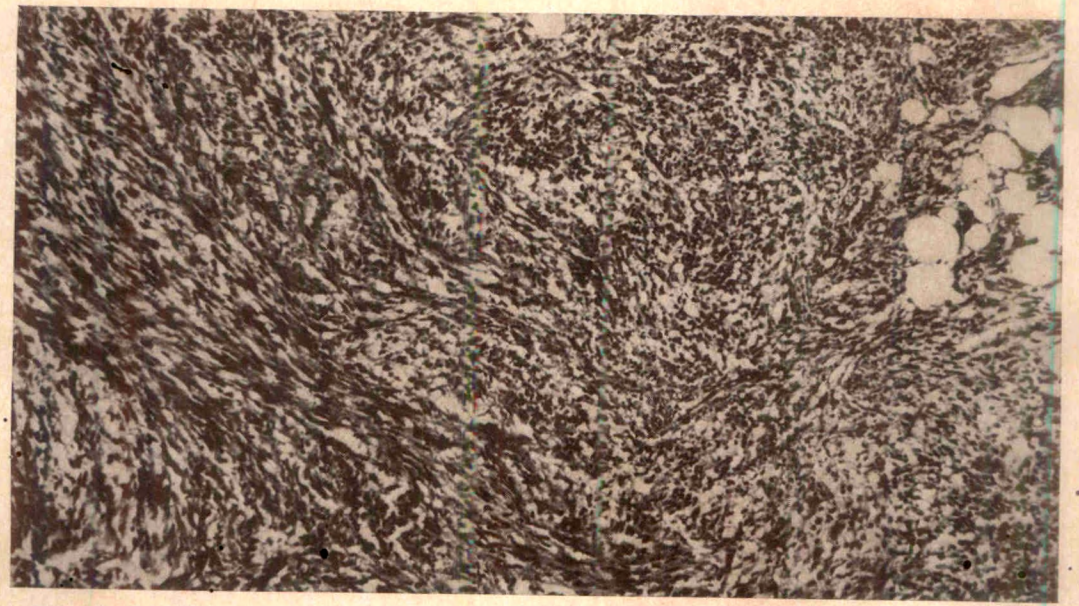


Fig. 14 (Jakobiec and associates). Case 5. Rhabdomyosarcoma. A bundle of tumor cells on the left displays nuclear palisading. The tumor has invaded the orbital fat above and to the right. The cells are loosely arranged; note the absence of a conspicuous vascular component (hematoxylin and eosin, ×120).

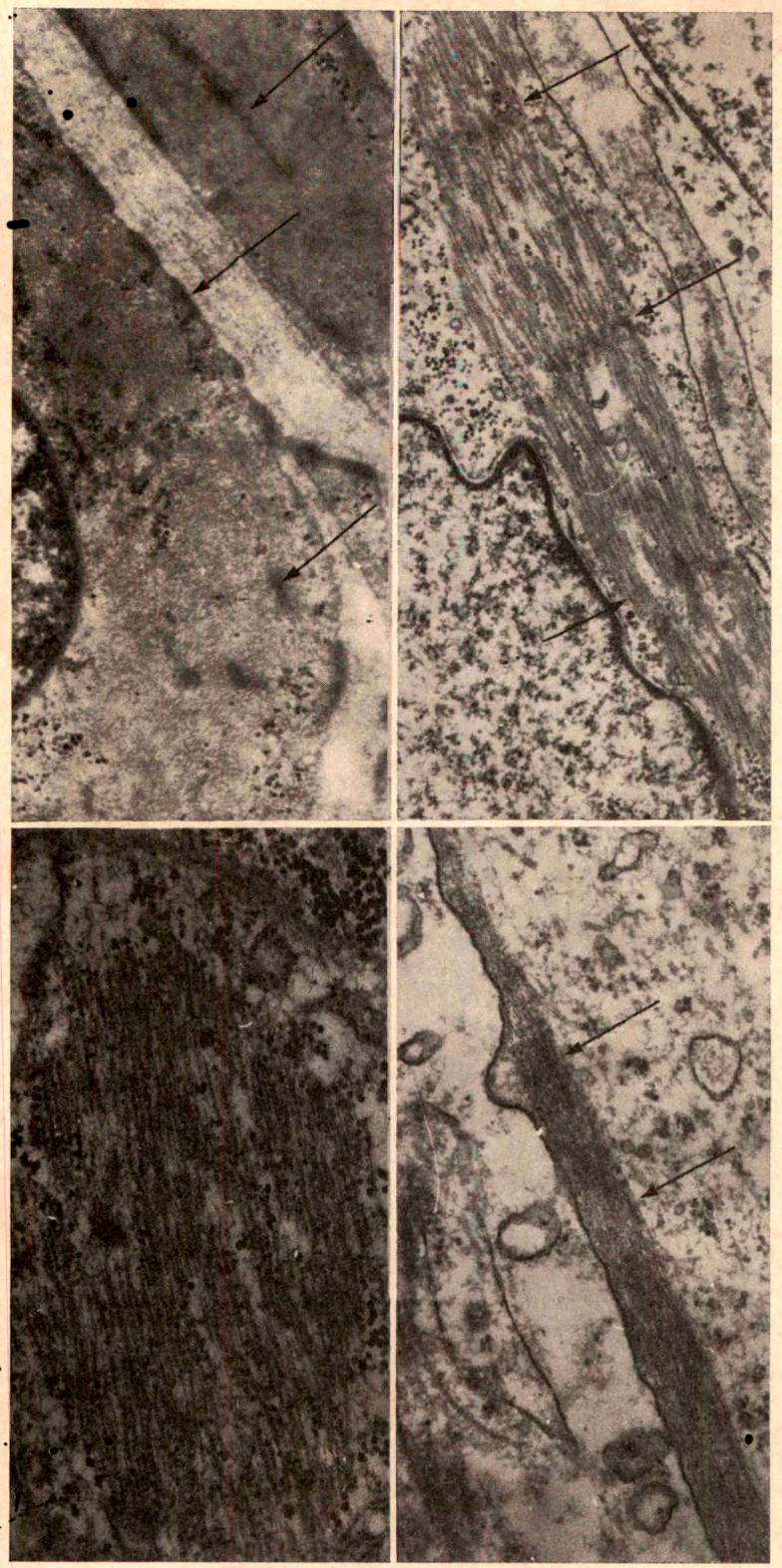


Fig. 15 (Jakobiec and associates). Upper left, Leiomyoma. The cytoplasm is filled with indistinct thin filaments. Arrows point to fusiform densities and plasmalemmal densities (×6,000). Lower left, Thick filaments without sarcomeric organization in a rhabdomyoblast (×18,000). Upper right, Abortive sarcomere composed of thick filaments. Arrows point to incomplete transverse Z-lines (×18,000). Lower right, Subplasmalemmal actin filaments (arrows) are found in the peripheral cytoplasm of fibrocytoid cells in embryonal rhabdomyosarcoma. The oval outlines on the left are small cell processes (×18,000).

typical history of an abrupt and rapidly progressive proptosis and a radiosensitive tumor.[8]

Two contrasting clinical features of leiomyoma and leiomyosarcoma should be emphasized (Table). The first is that the benign tumor presents in younger individuals and the malignant tumor develops in older patients. In the previous reports, the patients with leiomyomas have been aged 9 years,[3] 17 years,[4] 18 years,[1] and 41 years.[2] Second orbital enlargement was seen on x-ray studies of the two orbits harboring the leiomyosarcomas, indicating a long-standing process, and perhaps pointing to the origin of the sarcoma from a preexistent benign lesion. However, weighing against this last possibility are the clinical and pathologic observations that the more frequently encountered malignant smooth muscle tumors of the uterus and gastrointestinal tract arise de novo rather than as malignant degenerations of benign lesions.

The histologic diagnoses of orbital leiomyoma and leiomyosarcoma were established by the demonstration of nonstriated cytoplasmic filaments with the trichrome stain. In our cases, the tissue from the first biopsy contained cells with convincing cytoplasmic filaments and deeply staining red cytoplasm. Besides their cytoplasmic filaments, the benign tumor cells were arranged in bundles or fascicles that often displayed palisading of nuclei with blunt or rounded ends. Reticulin fiber deposition occurred as thick spiraling fibers around the benign tumor cell fascicles, but as irregularly distributed fibers in the malignant tumors. The benign tumors were encapsulated, although small satellite or daughter nodules frequently projected from the main tumor mass. The leiomyosarcomas, on the other hand, were incompletely encapsulated and invaded the orbital fat and musculature. Nuclear pleomorphism, hyperchromatism, and most importantly, numerous mitoses distinguished the leiomyosarcomas. Even small numbers of mitoses in a smooth muscle tumor should be alarming.

The vascular patterns that were found in

TABLE

SUMMARY OF CASES

Case No.	Age (yrs), Sex	Diagnosis	Initial Presenting Signs and Symptoms	Duration of Symptoms	Location of Mass	X-ray Studies	Outcome
1	17, M	Leiomyoma	Visible mass	2 mos	Right orbit; medial canthal area, extraconal, periosteal	Unremarkable	No recurrence 16 yrs after local excision
2	34, F	Leiomyoma	Sinusitis; 6 mm proptosis; diplopia; 2 mm blepharoptosis; slight papilledema	2 yrs	Left orbit; posterior intraconal, perioptic mass extending through superior orbital fissure to anterior cranial fossa	Increased soft tissue density; widening of superior orbital fissure	Recurred 7 yrs after local excision and was radiated; radiation induced malignancy developed and metastasized to kill patient 17 yrs after initial presentation
3	58, F	Leiomyosarcoma	↓ Visual acuity; 3 mm proptosis; dilatation of nasal episcleral vessels; papilledema; choroidal striae	15 mos	Right orbit; nasal, intraconal	Symmetrical enlargement of orbit	Died of metastases 15 mos after excision by Krönlein orbitotomy
4	59, F	Leiomyosarcoma	9 mm proptosis; unable to look down	18 mos	Left orbit; intraconal, inferior temporal	Symmetrical enlargement of orbit	Died of metastases 1 yr after last of 5 orbital excisions, 7 yrs after initial presentation
5	7, F	Rhabdomyosarcoma	2 mm proptosis; rapid course	1 wk	Right orbit, inferior portion	Unremarkable	No recurrence 1 yr after radiotherapy

all four tumors are a trademark of orbital smooth muscle neoplasms. In the benign tumors there were fields of pseudohemangiopericytomatous arrangement (Fig. 8), wherein interanastomosing clefts were surrounded by tumor cells. In the two malignant tumors, somewhat different patterns were seen. In one, ectatic vascular spaces, sometimes containing tumor cells that had erupted in the lumen (Fig. 12), perforated the tumor tissue including the metastatic deposits; in the other, striking spherules of tumor cells laminated around small capillaries often detaching at the periphery from the main tumor mass (Fig. 9).

The autopsy material from Case 4 showed bizarre cellular forms and loss of differentiation, both to such an extent that the diagnosis of leiomyosarcoma was totally obscured. A diagnosis would not have been possible without access to the prior biopsy material.

The behavior of leiomyoma is not minatory. On the other hand, leiomyosarcoma is much more dangerous—more so than primary orbital fibrosarcoma,[11] fibrous histiocytoma,[12] and hemangiopericytoma.[13] The highly malignant and unpredictable character of leiomyosarcoma has also been documented in other sites.[14]

The surgical treatment of leiomyoma consists of a wide surgical excision aimed at encompassing the satellite lobulations. The tumor is slow-growing, and if a portion is left behind, it is better to await a later recurrence than to irradiate, since the tumor is generally radioresistant.[4] Radiation indeed may transform a benign lesion into a sarcoma. In one patient (Case 2), whose encapsulated intraorbital tumor was completely removed, but whose transfissural intracranial extension could not be reached by the orbital approach, benign neglect or a craniotomy would have been preferable to the radiation she received. Vision was lost due to radiation damage to the globe, and a probable radiation-induced sarcoma supervened.

Once a diagnosis of leiomyosarcoma has been established, exenteration with the removal of any involved bone is required. Tomograms of the orbit should be performed in search of sites of erosion or invasion of bone. It is possible that asymptomatic metastases may have occurred before exenteration, owing to the highly malignant character of this neoplasm. Therefore, a meticulous search for metastases, especially tomography of any suspicious lung shadows, should be conducted before proceeding with exenteration.

The origin of smooth muscle tumors situated deep in the orbit is probably from immature vessel-associated cells,[15] a point that was discussed in an earlier publication.[4] There are constantly replicating primitive cells associated with blood vessels that could be the source of these tumors.[16,17] The leiomyoma in the present series (Case 2) that spanned the superior orbital fissure contributes further circumstantial evidence in favor of a vascular origin of these tumors, since many of the orbital veins pass through the superior orbital fissure. The case reported by Nath and Shukla[1] at the orbital apex, where only vascular smooth muscle is found, can be adduced as further evidence of the vascular origin of orbital smooth muscle tumors. The conspicuous histologic vascular patterns contained in orbital leiomyomas reinforce the impression that these tumors originate from vascular smooth muscle. It is theoretically possible, however, that some smooth muscle tumors of the anterior orbit may originate from Müller's muscle.

Furthermore, when smooth muscle tumors originate in other sites than the orbit where there is normally only vessel-associated smooth muscle—as in the sinuses[18] or oropharynx[19–21]—the tumors display striking vascular patterns, and are sometimes called angiomyomas or vascular leiomyomas. Leiomyomas of the skin are either solid or vascular, corresponding to their probable origins either from the arrectores pilorum or from vessel-associated musculature.

While there is now considerable evidence

that the fibroblast and smooth muscle cell are close mesenchymal relatives, and that in various pathologic conditions cells called myofibroblasts can be found combining features of both,[11,22] a similar close cytogenetic relationship has not been demonstrated between striated muscle and smooth muscle. Striated muscle tumors may arise in sites that normally do not contain striated muscle, but tumors containing both striated and smooth muscle are not known. Striated muscle appears to originate from a progenitor cell in a different mesenchymal compartment from that of the fibroblast and smooth muscle cell.[10]

The histogenetic separation between striated and smooth muscle is also fairly well maintained clinically and pathologically. Orbital rhabdomyosarcomas are rapidly developing tumors that occur preferentially in children in the first decade—usually around 7 or 8 years of age. Benign smooth muscle tumors occur in children and young adults; malignant smooth muscle tumors, like other nonembryonal sarcomas, occur in older persons. The clinical pace of benign smooth muscle tumors is not as fulminant as that of orbital rhabdomyosarcoma, and this can be useful clinically in distinguishing smooth muscle tumors from rhabdomyosarcomas in the pediatric age group, where there is a slight age overlap between the two tumors. In this context, the report by Begue and Mawas[5] of a leiomyosarcoma in a 6-year-old girl who developed proptosis over several days appears to us to be an embryonal rhabdomyosarcoma, closely resembling our Case 5.

Histologically, spindle cell embryonal rhabdomyosarcomas have elongated and narrower nuclei than those of smooth muscle cells, looser myxomatous areas along with more tightly bundled cells, and alveolar patterns.[8] Rhabdomyosarcomas also lack the distinctive vascular patterns seen in orbital smooth muscle tumors.

Our own data and a critical evaluation of Begue and Mawas'[5] case support the belief that any rapidly developing orbital tumor in a child that contains spindle cells with eosinophilic cytoplasm should be regarded as a rhabdomyosarcoma. Electron microscopy clearly demonstrated this in our Case 5, for despite the absence of cross striations by light microscopy, electron microscopy (Fig. 15) detected thick (150 nm) filaments with and without sarcomeric organization. Smooth muscle tumors by contrast have thin (60 nm) filaments with oval fusiform densities rather than the transverse Z-lines of striated muscle.

Summary

Comparison of the clinical and pathologic features of two orbital leiomyomas, two leiomyosarcomas, and one embryonal rhabdomyosarcoma showed that the leiomyomas occurred in young individuals and the leiomyosarcomas in older patients. The histopathologic diagnoses rested on the intense cytoplasmic eosinophilia and nonstriated longitudinal cytoplasmic filaments demonstrated by means of the trichrome stain. The leiomyosarcomas disseminated 15 months and seven years after their orbital presentations.

The treatment of both leiomyoma and leiomyosarcoma is surgical. Leiomyomas are encapsulated growths that may have small satellite nodules projecting from the main tumor mass; thus, a margin of normal tissue should also be excised, lest a small lobulation be left behind to serve as the seed for a late recurrence. Once the diagnosis of leiomyosarcoma has been made, and no evidence of metastasis has been found after a thorough systemic evaluation, the orbit should be exenterated, because the tumor is unencapsulated and liable to widespread dissemination.

Rhabdomyosarcoma has a much more fulminant course than leiomyosarcoma, and especially more so than that of leiomyoma of childhood. The histopathologic diagnosis of a malignant smooth muscle tumor in a child should always be questioned, since

embryonal rhabdomyosarcoma is a much more likely diagnosis.

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RETINAL HEMORRHAGES IN POSTERIOR VITREOUS DETACHMENT

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Vitreous and retrovitreal hemorrhages are noted in about 5% of patients with acute symptomatic posterior vitreous detachments without retinal breaks.[1-3] Presumably such hemorrhages are due to microtrauma to the retina at persisting vitreoretinal adhesions.[4] These are particularly strong about the optic disk, macula, vitreous base, and over retinal vessels.[5,6] Punctate retinal hemorrhages at the posterior border of the vitreous base are seen frequently.[4] Usually they accompany preretinal hemorrhages or retinal tears but may precede the latter.[2] A rarer complication of posterior vitreous detachment appears to be retinal hemorrhage around the optic disk and macula.

In 1914, Kraupa[7] made the first clinical recognitions of posterior vitreous detachment. In 1936 he[8] was also the first to note retinal hemorrhage in association with posterior vitreous detachment. He observed a striate hemorrhage near the optic disk of a 56-year-old myope. de Vries[9] described five patients with small peripapillary striate hemorrhages. All patients had biomicroscopically proven posterior vitreous detachments. Linder[1] and Jaffe[10] reported one case each. In a recently published series of 100 consecutive cases of spontaneous, posterior vitreous detachments, Wise[11] found four patients with small hemorrhages at the disk margin: in two instances striate and in two others blot hemorrhages.

All of the patients in these previously published cases had moderately severe myopia. The hemorrhages were small, striate, and generally near the optic disk. In no case was visual acuity impaired by the hemorrhage. Symptoms were the acute onset or aggrevation of entoptic phenomena with or without light flashes.

We saw four patients with retinal hemorrhage at the posterior pole of the eye due to posterior vitreous detachment. Morphologically, these cases differ radically from the small, single, peripapillary, striate hemorrhages previously described. Retinal hemorrhages due to posterior vitreous detachment in our patient were strikingly large, multiple, and, when involving the macula, caused temporary visual loss.

CASE REPORTS

Case 1—A 44-year-old man noted "spots" in his left superior nasal field. There were no light flashes. Visual acuity was 20/15 in each eye. The patient's refractive error was R.E.: −7.00 +1.00 at 95°, and L.E.: −8.50 +1.00 at 90°. Visual field testing using the Goldmann perimeter was normal. The pupils were equal in size. There was no afferent pupillary deficit. Slit-lamp examination of the anterior segment of both eyes was normal. Red blood cells were dispersed in the vitreous body of the left eye and a posterior vitreous detachment was present in each eye. Intraocular pressure was 19 mm Hg in each eye. Retinal vessels and circulation appeared normal. A large striate retinal hemorrhage covered most of the optic disk in the left eye (Fig. 1). There was an associated subretinal hemorrhage surrounding the disk. Ophthalmoscopy and biomicroscopy failed to reveal any retinal tear or bleeding site. Myopic conus was present in each eye. The fundus of the right eye was otherwise normal.

The patient's general health was normal without evidence of diabetes, hypertension, renal or cardiac disease. Hematologic examination including complete blood count (CBC), platelet count, bleeding time, prothrombin time, sedimentation rate, and coagulation time was normal. There was no history of Valsalva maneuver. The hemorrhage resolved completely during the next two months. The patient was seen annually since then. Visual acuity was 20/15 in each eye. The fundus was normal. There was no sign of drusen of the optic disk.

Case 2—A 33-year-old man in good health without diabetes or hypertension was first examined in 1967 for the purpose of obtaining contact lenses. Visual acuity was 20/15 in each eye. The refractive error was R.E.:−5.50 +0.50 at 180°, and L.E.:−6.25 +0.25 at 180°. Both corneas, anterior chambers, irides, lenses, retinas, and optic disks were normal. No mention was made of a posterior

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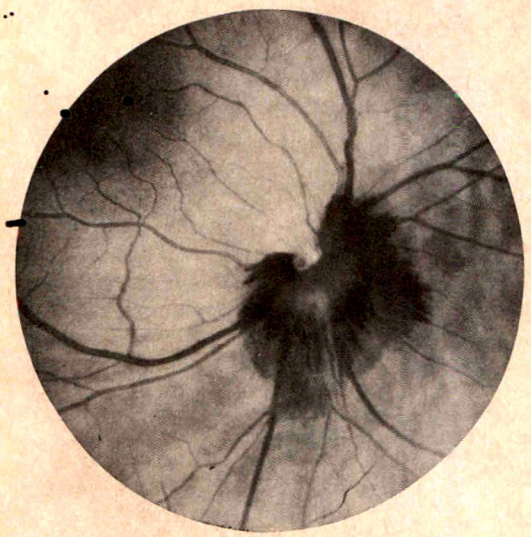


Fig. 1 (Cibis, Watzke, and Chua). Papillary and peripapillary striate retinal hemorrhage. There is an associated subretinal hemorrhage.

vitreous detachment. On May 18, the patient noted distortion of his vision and an increase in "floaters" in his right eye. There were no light flashes. The symptoms began that morning while taking an examination. There was no history of a Valsalva maneuver. Visual acuity was 20/15 in each eye. There was no afferent pupillary defect. Intraocular pressures were R.E.: 12 mm Hg, and L.E.:10 mm Hg. Biomicroscopic examination of the cornea, iris, anterior chamber, and lens was normal in each eye. There were no cells or flare in the anterior chamber. The right optic disk was totally obscured by a striate retinal hemorrhage with an associated preretinal and subretinal hemorrhage (Fig. 2). Ophthalmoscopy and biomicroscopy failed to reveal any retinal tear or bleeding site. There was a posterior vitreous detachment in each eye. Examination of the left fundus was normal. Hematologic examination including CBC, platelet count, bleeding time, clotting time, and prothrombin time was normal. The hemorrhage resolved in the next month, the preretinal component being the last to disappear. The patient was last seen ten months after the hemorrhage. Examination of both eyes was normal, visual acuity was 20/15 in each eye, and there was no sign of optic disk drusen.

Case 3—A 43-year-old white man noted decreased vision with increased entoptic phenomena in his right eye beginning five days earlier. There were no light flashes. Visual acuity was R.E.:20/20, and L.E.:20/25. The refractive error was R.E.: −13.00 +2.00 at 114°, and L.E.:−14.00 +1.25 at 68°. Biomicroscopic examination of the cornea, anterior chamber, and iris was normal. There was no afferent pupillary defect. Intraocular pressures were R.E.: 18 mm Hg, and L.E.: 28 mm Hg. Retinal veins in the right eye were slightly congested and tortuous. Numerous blot hemorrhages were scattered throughout the fundus (Fig. 3). Ophthalmodynamometry was equal in the two eyes. The right eye had a posterior vitreous detachment, the left eye did not. On visual field examination the patient demonstrated nasal visual field loss in each eye. Gonioscopy revealed an open chamber. The patient was placed on antiglaucoma therapy and followed by the referring ophthalmologist. Six months later he was re-referred because of a retinal detachment secondary to a retinal tear at the vitreous base in the left eye. The hemorrhages in his right eye were no longer present. Visual acuity was R.E.:20/20, and a posterior vitreous detachment was present in the left eye. One year after first presenting with retinal hemorrhages due to posterior vitreous detachment in the right eye, visual acuity was R.E.:20/25. There were no further hemorrhages.

Case 4—A 46-year-old white woman was first seen in 1964 with a two-months' history of blurred vision in her right eye. Visual acuity was R.E.: 20/25, and L.E.: 20/30. The refractive error was R.E.:−6.00 +1.50 at 90°, and L.E.:−7.25 +1.00 at 90°. Myopia with lattice degeneration of the retina in each eye and vitreous detachment in the right eye was diagnosed. In 1971 the patient had an episcleral buckling procedure in the left eye for a limited retinal detachment due to two retinal tears at the edges of a patch of lattice. Visual acuity was 20/25 in the operated eye. Intraocular pressures were R.E.: 22 mm Hg, and L.E.: 23 mm Hg. Visual fields using a Goldmann perimeter were normal. The patient was seen twice yearly for the next three years and showed no change. On Nov. 8, 1974, she complained that vision in her left eye had become blurred four days earlier. She now had

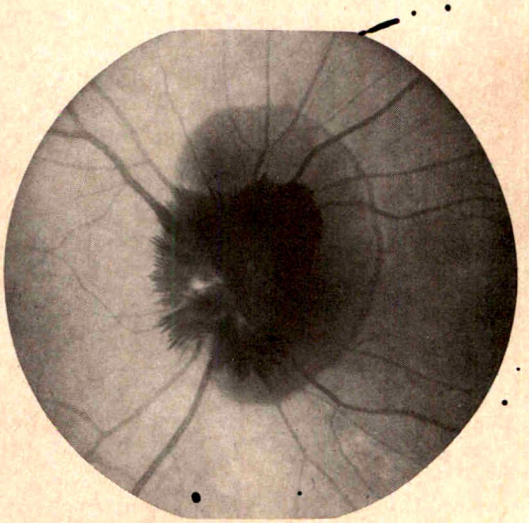


Fig. 2 (Cibis, Watzke, and Chua). Striate retinal hemorrhage totally obscuring the right optic disk. There is an associated subretinal as well as preretinal hemorrhage.

a prominent prepapillary glial ring in the midvitreous with a small retinal hemorrhage in the macula (Fig. 4). The retinal periphery was unchanged from previous examinations. No vessels that could have bled were seen at the old retinal tears nor were any new retinal tears or vitreal hemorrhages found. Visual acuity was 20/100 in the left eye. A diagnosis of posterior vitreous detachment with acute macular hemorrhage was made. The macular hemorrhage resolved and the patient's visual acuity returned to 20/25 over the next two months.

Discussion

Retinal tears and vitreous hemorrhages are accepted complications of acute detachment of the posterior vitreous. They are presumed consequences of microtrauma to the retina and retinal vessels at sites of particularly intimate vitreoretinal adhesion. Since the same pathogenesis should logically produce retinal hemorrhages it is surprising that except for punctate hemorrhages at the vitreous base these have rarely been reported.

The patients with retinal hemorrhages due to posterior vitreous detachment have some noteworthy features. Two patients (Cases 1 and 2) had massive retinal hemorrhages overlying the optic disks without loss of acuity or visual field. The retinal hemorrhages in another patient (Case 3) with posterior vitreous detachment were not isolated but were multiple. The fourth patient (Case 4) had vision loss because of a macular hemorrhage; visual acuity returned to normal after the hemorrhage resolved. In no instance was a retinal tear or site of injury to vessels noted by indirect ophthalmoscopy or meticulously performed biomicroscopy.

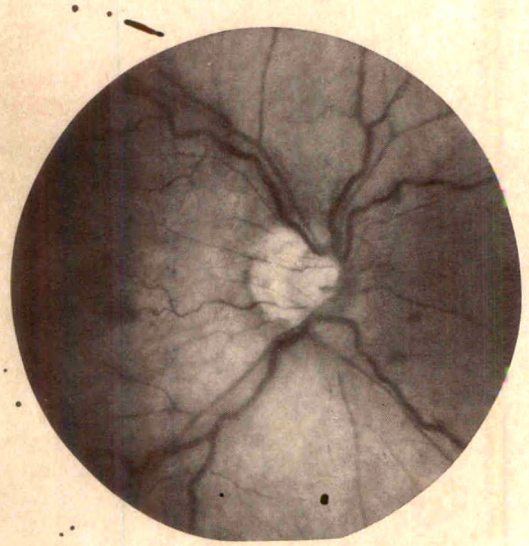


Fig. 3 (Cibis, Watzke, and Chua). Multiple small punctate hemorrhages throughout the posterior pole. There is some tortuosity of retinal vessels.

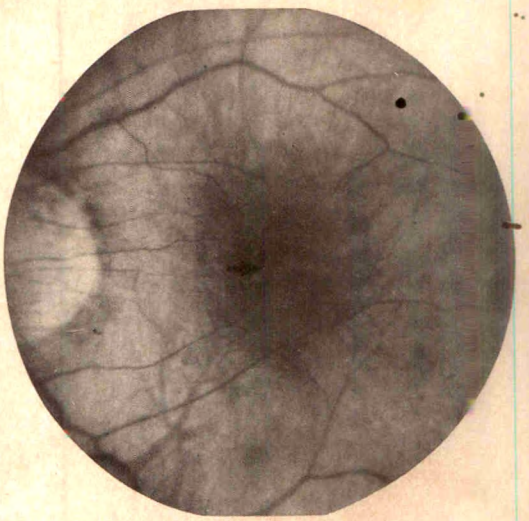


Fig. 4 (Cibis, Watzke, and Chua). Macular hemorrhage (arrow) that caused temporary visual loss. Visual acuity was 20/100. A light reflex from the camera is seen immediately above the arrow.

All of our patients had moderately severe myopia. In three patients, the only symptoms were those of posterior vitreous detachment (Cases 1-3). We saw the fourth patient frequently and the prominent glial ring in the midvitreous was not present until the macular hemorrhage appeared. We feel this is a well-documented instance of a partial vitreous detachment causing a retinal tear that three years later evolved into a total posterior vitreous detachment with a macular hemorrhage and a prepapillary glial ring. The acuteness of the vitreous detachment was diagnosed by history in the other cases.

Published reports[1-3,11] dealing with complications of posterior vitreous detachment list these as (1) retinal tears, (2) vitreoretinal traction at the posterior pole, and (3) intravitreal and retrovitreal hemorrhage.

We suggest that retinal hemorrhages should be added to this list of complications.

Summary

Detachment of the posterior vitreous can cause clinically significant retinal hemorrhage. Two patients with acute posterior vitreous detachment had massive retinal hemorrhages overlying the optic disks. These absorbed in time without sequelae. A third patient had numerous small blot hemorrhages scattered near the optic disk and macula. A fourth patient presented with a small macular hemorrhage causing temporary visual loss. All patients had moderately severe myopia and were in good health without hypertension or diabetes. There was no history of trauma or Valsalva maneuver. Hematologic and coagulation studies were normal. These cases indicate that retinal hemorrhages due to posterior vitreous detachment may be strikingly large, multiple, and, when involving the macula, cause temporary visual loss.

Acknowledgment

Russell H. Watt, M.D., Wolfe Eye Clinic, Marshalltown, Iowa, referred a patient (Case 1).

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GYRATE ATROPHY OF THE CHOROID AND RETINA WITH HYPERORNITHINEMIA

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Gyrate atrophy of the choroid and retina is a rare disease that has been linked to a specific biochemical abnormality, hyperornithinemia.[1,2] Hyperornithinemia has previously been observed in syndromes with completely different clinical presentations. Detailed examination of cases of gyrate atrophy may give rise to the understanding of the more common retinal pigmentary dystrophies, such as retinitis pigmentosa and choroideremia. The fundamental causes of this whole group of diseases remain undefined. Therefore, we have examined in depth the medical, ophthalmologic, and biochemical aspects of a single case of gyrate atrophy.

CASE REPORT

A 28-year-old man was a fourth child, having two elder sisters; one child had died at birth of unknown cause. The patient had been breast fed. During his early weeks his stools were abnormal, but these cleared. He had a "slight cerebral palsy" at birth and what his parents considered to be a peculiar manner of walking until 11 years of age. His limbs were very thin but developed normally after puberty and his general state of health was satisfactory thereafter. He attained a grade 12 level at school, then qualified as a surveyor. He is married, but has no children.

He was first seen in February of 1974, complaining of loss of vision. He stated that since the age of 9 years he had worn spectacles; during his teens he had noticed reduction of vision at night, which had gradually become noticeable as a loss during the daytime and a tendency to bump into objects. Since the age of 23 his visual acuity had been gradually decreasing and by the age of 28 he had difficulty reading.

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Presented at the 111th meeting of the American Ophthalmological Society, the Homestead, Virginia, May 30, 1975.

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Family history contained no evidence of familial disease, either metabolic or ocular. Both parents and the two sisters were healthy, and had no ocular complaints. There was no indication of consanguinity (Fig. 1). An uncle, on his father's side had a retinal detachment.

General physical examination revealed no abnormality apart from the eyes. Height was 180 cm, weight 65.3 kg, and in bodily habitus he was tall, slender, and normally proportioned. The thyroid gland was palpable but normal in size. The palate had a high arch. The chest and cardiovascular system showed no abnormality: blood pressure was 120/70 mm Hg, the pulse 74 beats per minute at rest, and regular. The precordium was normal. The liver and kidney were not palpable. The genitalia and secondary sexual characteristics were normal. No scoliosis was present, and apart from the feet having a high longitudinal arch, the skeletal system and musculature were normal. Testing of general knowledge, abstract thinking, calculation, and memory indicated no deficit. There was no aphasia. All modalities of sensation were normal, as were tests of motor power, muscle tone, and coordination. Deep tendon reflexes were active and symmetrical. Thus no aspect of the clinical neuromuscular examination was abnormal. He showed the signs of onychophagia. There was a brownish area of pigmented skin on the abdomen.

His eyes appeared superficially normal. They were straight, with a small exophoria; convergence was good. Ocular mobility was full. Corneal sensation and orbicularis actions were intact. The pupils were slightly irregular but equal and responsive to light. There were no adhesions to the lens in either eye. There was a posterior subcapsular opacity in both lenses. The vitreous body was degenerate and fibrillar. It was possible to see both fundi. There were regular rows of large, lacunar atrophy, marginated by strands of pigment, extending from about

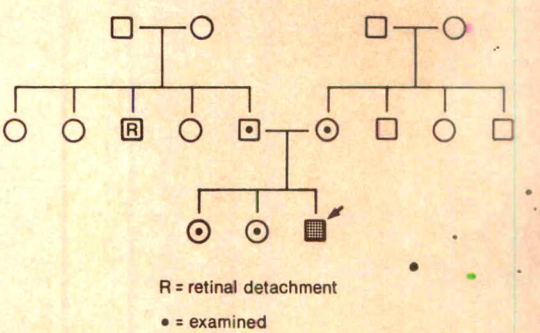


Fig. 1 (McCulloch and Marliss). Family pedigree.

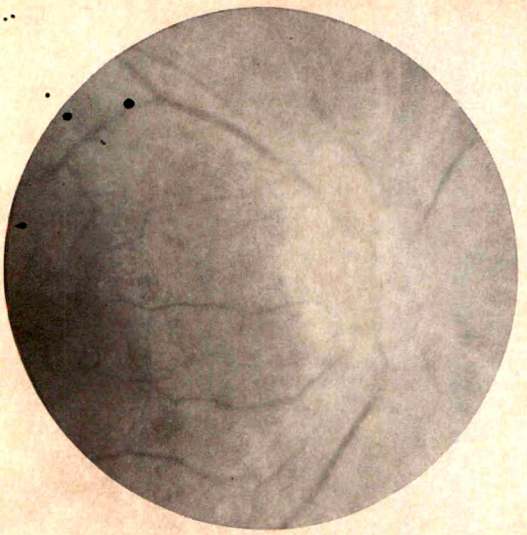


Fig. 2 (McCulloch and Marliss). Right eye, posterior pole.

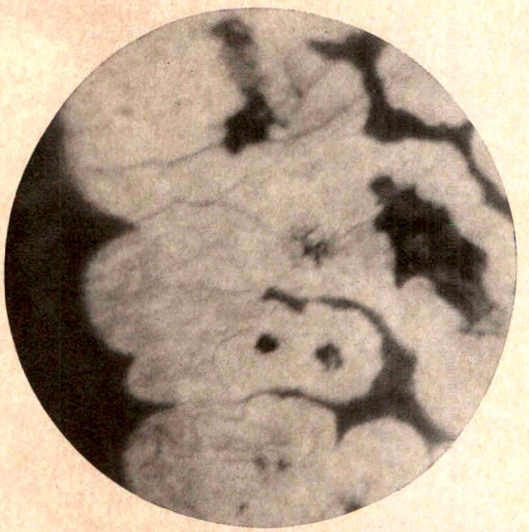


Fig. 3 (McCulloch and Marliss). Right eye, mid-periphery.

30 degrees from the macula, toward the periphery. The periphery was heavily pigmented. There was some choroidal sclerosis neighboring the disk but otherwise the central region was intact. The retinal vessels were narrowed. The optic disks were waxy pale, although not to the extent one might expect in retinitis pigmentosa (Figs. 2-5).

Visual acuity was 10/400 with either eye. Refraction with 1% cyclopentolate was R.E.: $-6.50 = 20/100$; L.E.: $-8.50 + 1.00 \times 90 = 20/100$.

In November 1974, the visual fields of both eyes were seen to be grossly restricted to finger movement (Fig. 6).

Color vision was tested for each eye by using the H-R-R plates, the Farnsworth D15 and 100 hue tests, and the anomaloscope. The patient displayed normal trichromatic vision.

Dark adaptation tested on the Goldmann adaptometer showed a slow cone threshold, elevated 1 log unit, and a rod threshold elevated 2.0 log units for the right eye, 1.5 log units for the left eye (Fig. 7).

The electroretinogram for each eye appeared extinguished. On summing 20 responses a dark adapted level of 10 μV or less was calculated. The visual evoked response was flat for a patterned stimulus and was low and delayed for a flash.

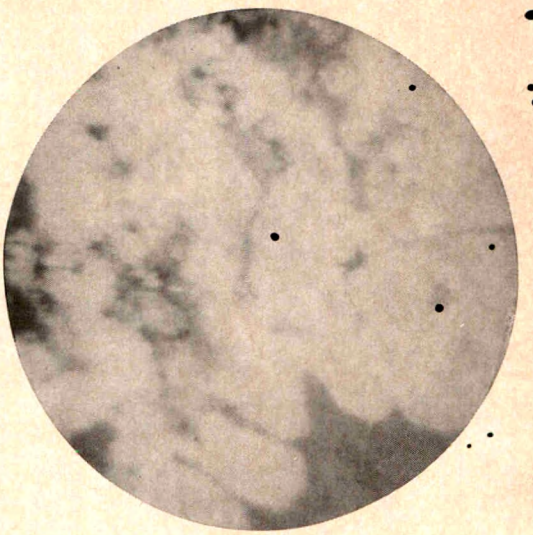


Fig. 4 (McCulloch and Marliss). Right eye, periphery.

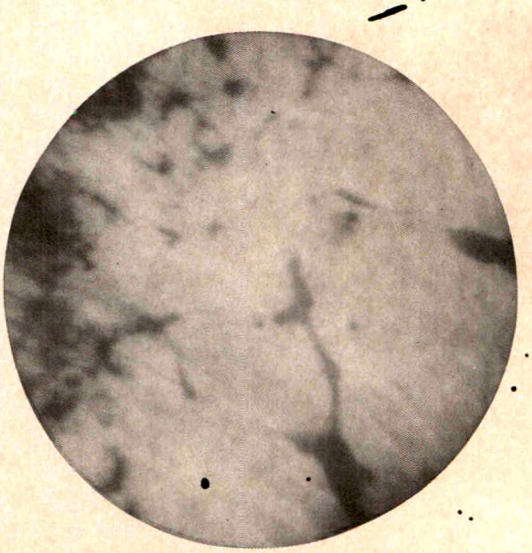


Fig. 5 (McCulloch and Marliss). Left eye, periphery.

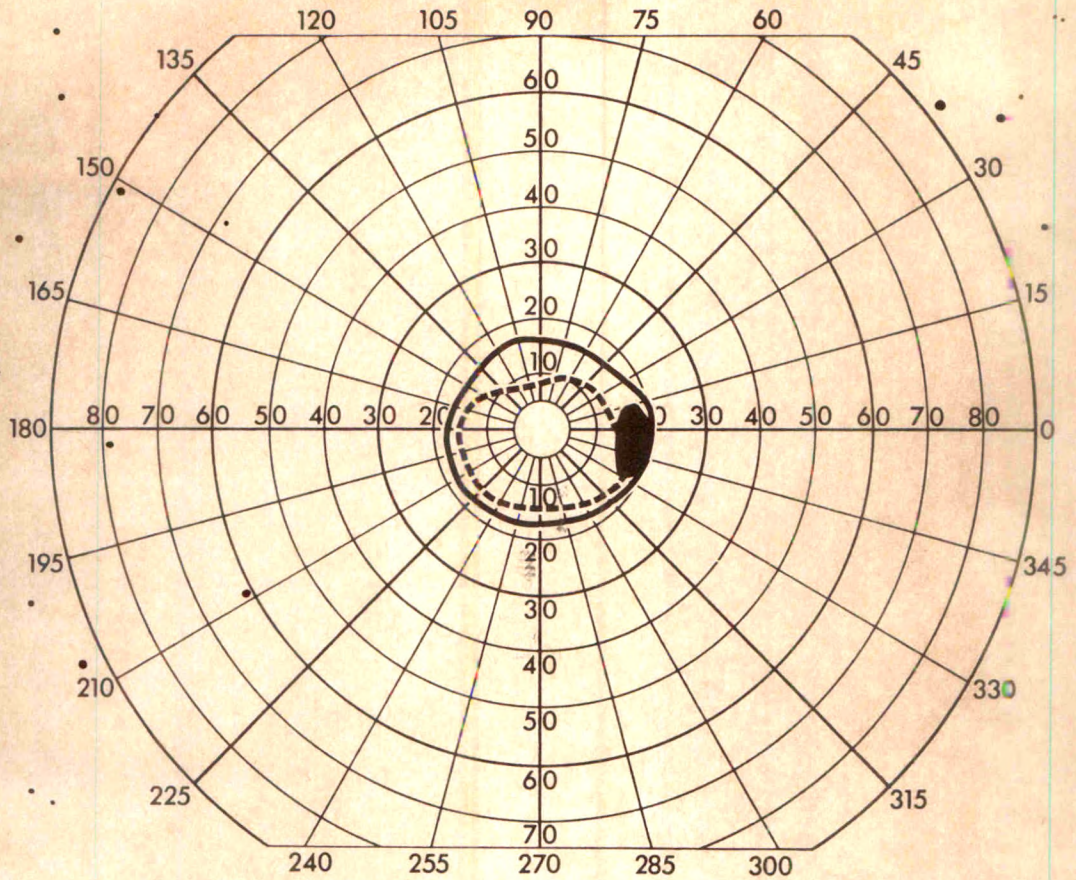


Fig. 6 (McCulloch and Marliss). Visual field of right eye. Field of the left eye corresponded to that of the right eye.

An ophthalmic examination was done on his two sisters, his mother, and father. All were essentially normal. Each one had 20/20 visual acuity in either eye with correction. The mother had some slight peripapillary atrophy, but otherwise the disks and fundi were normal. Her fields to a 3/1000 white test object showed a slight peripheral constriction. The fundi of the father and sisters were completely normal; their visual fields to a 3/1000 white test object were normal. Color vision of the parents and of the younger of the sisters was normal.

Cataract extraction was done on the patient's right eye in February 1974, and on his left eye in September 1974. Both were intracapsular extractions through a round pupil, with the aid of zonulysis. On both occasions the vitreous body was liquid and followed the lens. However, there was no trouble in clearing the anterior chamber and filling it with air. Healing was uneventful and a round pupil was obtained in both eyes. One small strand of vitreous touches the wound in the left eye. His refraction in March 1975 was R.E.: + 7.00 + 1.00 × 180 = 20/40; L.E.: + 7.00 = 20/40.

The lenses were sectioned and showed, anteriorly, some atrophy of the lens epithelium and some liquefaction of the lens fibers. Posteriorly, there were a number of bladder cells and some liquefactive degeneration.

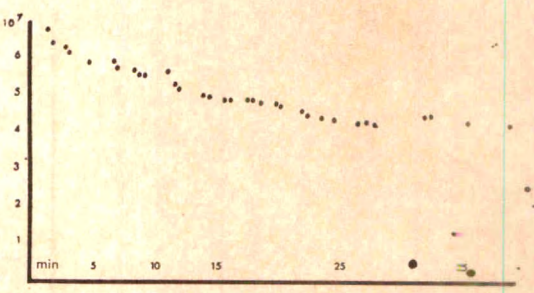


Fig. 7 (McCulloch and Marliss). Dark adaptation curve of the right eye, using the Goldmann adaptometer.

Results

All of the following standard clinical laboratory tests yielded normal findings: complete hemogram, urinalysis, VDRL, and blood biochemistry (serum electrolysis and CO_2, serum bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, lactate dehydrogenase, serum protein, electrophoresis, blood urea nitrogen, serum creatinine and creatinine clearance, and serum cholesterol and triglycerides). Serum creatine phosphokinase was not elevated and 24-hour urine creatine was normal. The serum uric acid levels were 8.9, 8.1, 8.4, and 10.6 mg/100 ml in four of seven tests. Normal is below 8.0 mg/100 ml. The 24-hour uric acid excretion was normal. Cerebrospinal fluid showed normal protein and glucose and no cells.

The electrocardiogram showed no abnormalities, and the chest and skull roentgenograms were normal. An electromyogram and nerve conduction studies (median nerve) were similarly normal. However, in the electroencephalogram there was some spontaneous diffuse slowing and paroxysmal slow wave activity during hyperventilation. This was interpreted as suggestive of an epileptic diathesis. There was no sharp wave activity, nor were focal or localizing features present.

Detailed psychometric testing showed his full scale IQ was 109, verbal 116, and performance 99. There were no focally low scores in the various subtests. He was low on tests of rapid visual-motor coordination and of memory for verbal material. Hence, his general level of functioning was average to high average.

A biopsy specimen from the right quadriceps femoris muscle showed a group of abnormal morphologic characteristics. On hematoxylin and eosin staining a portion of the muscle fiber appeared pale pink and amorphous. Histochemistry showed this alteration to be confined to type 2 (glycolytic) muscle fibers. The abnormality was associated with mild to moderate atrophy of some of the affected fibers. There was no inflammatory or fibrotic change or areas of necrosis or of regeneration present. The interstitial tissue, including the vessels, was normal. In the type 2 fibers activity was demonstrated to nicotinamide adenine dinucleotide-tetrazolium reductase but not for succinate tetrazolium reductase. The ratio of type 1 to type 2 fibers was low, with a relative increase in type 2 fibers. There was atrophy involving both type 1 and type 2, but more extensive in the latter. Electron microscopy showed large and small aggregates of linearly arrayed tubular structures which were not membrane bound (Figs. 8 and 9). These were identified as "tubular aggregates," as described by Engel, Bishop, and Cunningham.[3]

Individual amino acids were determined in body fluids deproteinized in an equal volume of 10% (wt/vol) perchloric acid, by automated ion exchange chromatography, using a Beckman 120C Amino Acid Analyzer. An accelerated procedure for determination of basic amino acids in physiologic fluids in three hours was used for many of the determinations. Normal values are drawn from our laboratory or from published data using similar analytic techniques in adult patient populations.

Figure 10 shows the levels of plasma acidic and neutral amino acids in our patient and normal values for comparison. Figure 11 shows the plasma and cerebrospinal fluid values for basic amino acids in this patient and normal values for comparison; apparently, there was a gross elevation of plasma ornithine levels. Marginal elevation of histidine and arginine was also found. Corresponding to the findings of Takki,[1] a slight decrease in lysine level was present. The cerebrospinal fluid showed a twentyfold increase in ornithine, and a significant elevation of arginine. The levels of the remainder of the amino acids in the cerebrospinal fluid were normal. Renal clearance of ornithine was normal (0.89 ml/min), but the total amount appearing in the urine approximated 5 mM daily.

The results of an oral glucose tolerance test (75 g) are shown in Figure 12. The peak value and that at two hours for whole blood glucose are diagnostic of diabetes mellitus. However, the blood ornithine levels declined during the provoked hyperglycemia.

To provide indirect information on the interconversion of arginine and ornithine, a 10-g dose of arginine monohydrochloride was administtered intravenously over ten minutes (Fig. 13). The transient elevation of blood arginine levels to greater than 2,000 μM was associated with a rapid rise in blood ornithine to 2,500 μM by 30 minutes, but followed by a decline toward preinfusion level, though it remained elevated up to 120 minutes.

A study was performed to determine the site or sites of origin of circulatory ornithine. In subjects with normal levels of ornithine, arteriovenous differences across muscle beds (forearm or leg), kidney, and splanchnic circulation are undetectable.[4-6] Figure 14 demonstrates the plasma arteriovenous differences, with normal values for comparison. The values for alanine indicate that it is normally released from muscle and kidney, and taken up by the liver. In contrast, in our patient ornithine showed a dramatic output from all the sites examined, and in amounts exceeding the output of alanine from muscle and kidney. These findings suggest that a generalized disorder involving ornithine metabolism exists in the patient.

Amino acid analyses were performed on

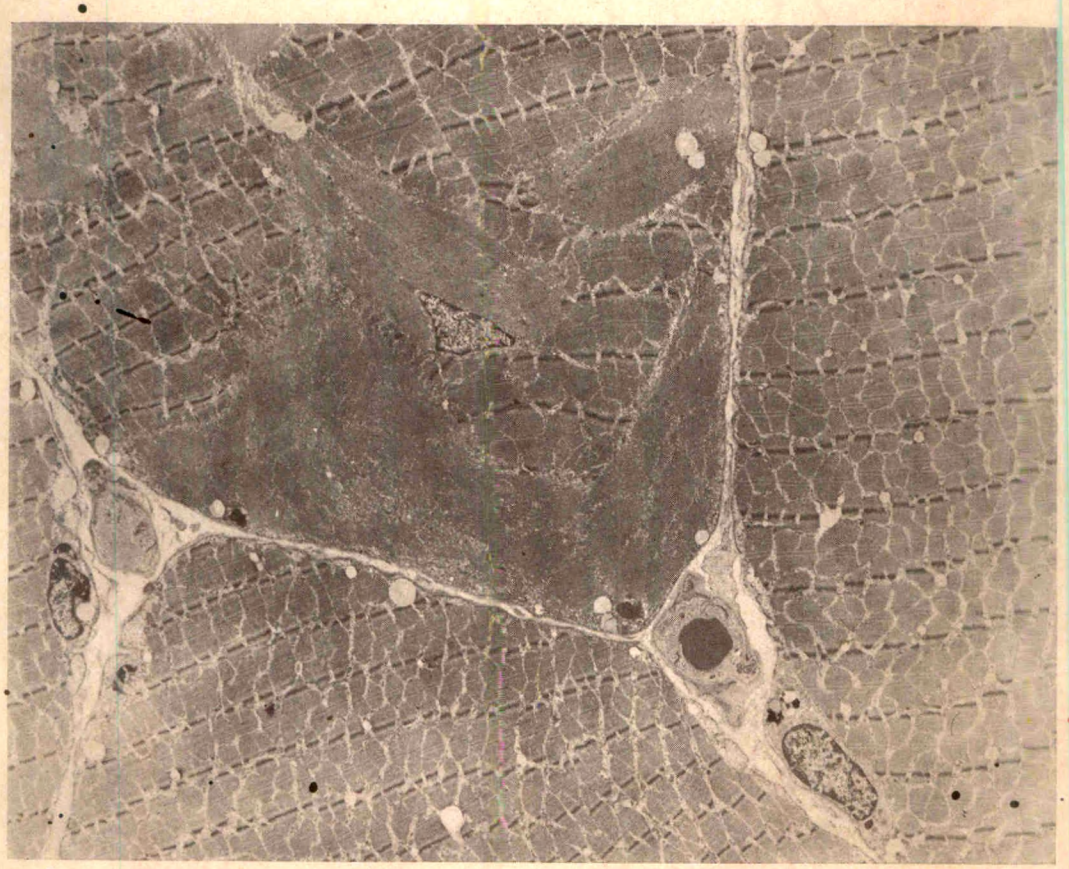


Fig. 8 (McCulloch and Marliss). Low-power electron micrograph of muscle showing aggregates of material in fibers (×3,600).

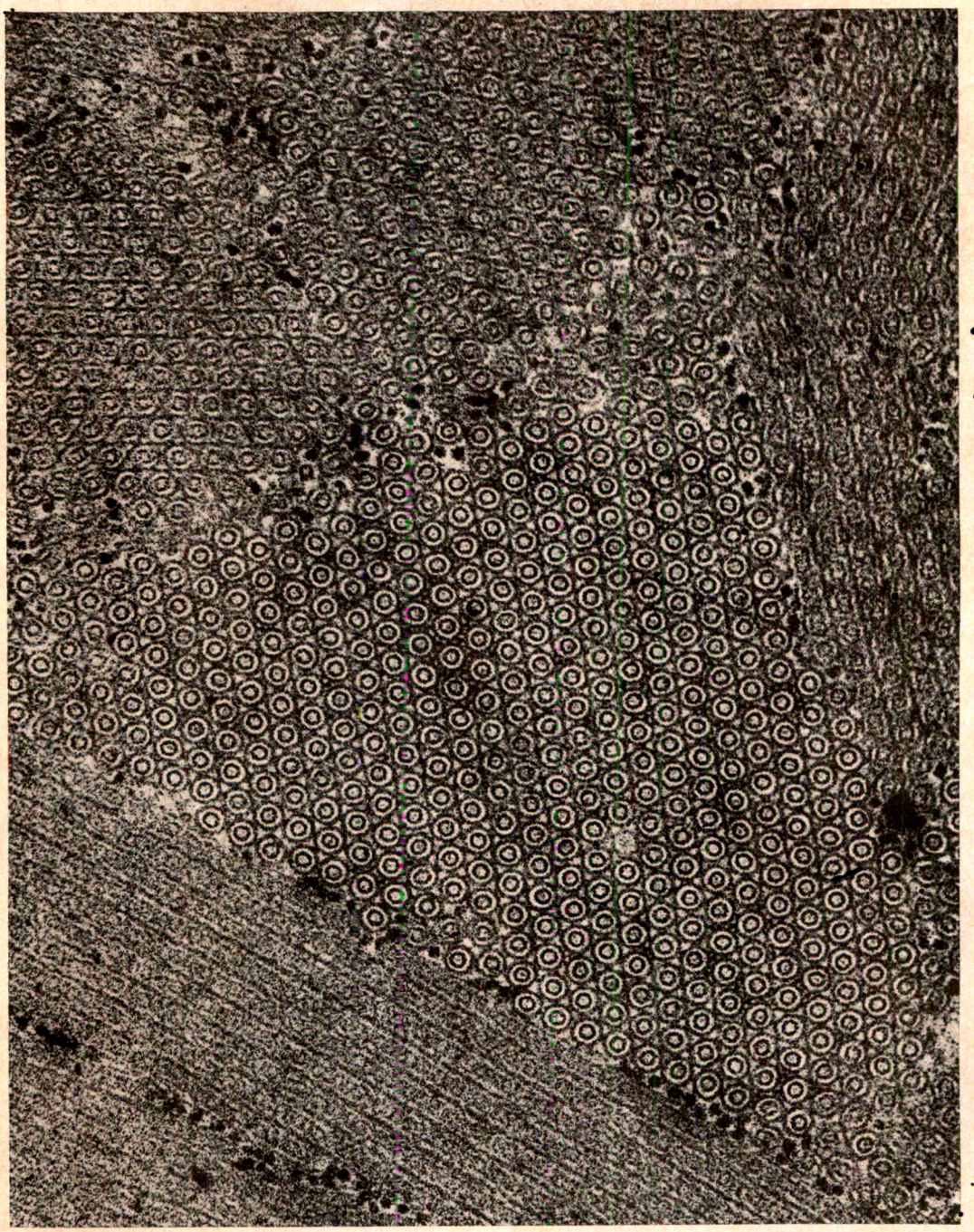


Fig. 9 (McCulloch and Marliss). High-power electron micrograph of aggregates showing their tubular structure (×72,000).

Fig. 11 (McCulloch and Marliss). Gross elevation of ornithine (ORN) levels in plasma and cerebrospinal fluid (CSF). Slight elevation of histidine (HIS) in plasma and slight elevation of arginine (ARG) in plasma and cerebrospinal fluid; LYS designates lysine level; normal (open bars) and our patient (shaded bars).

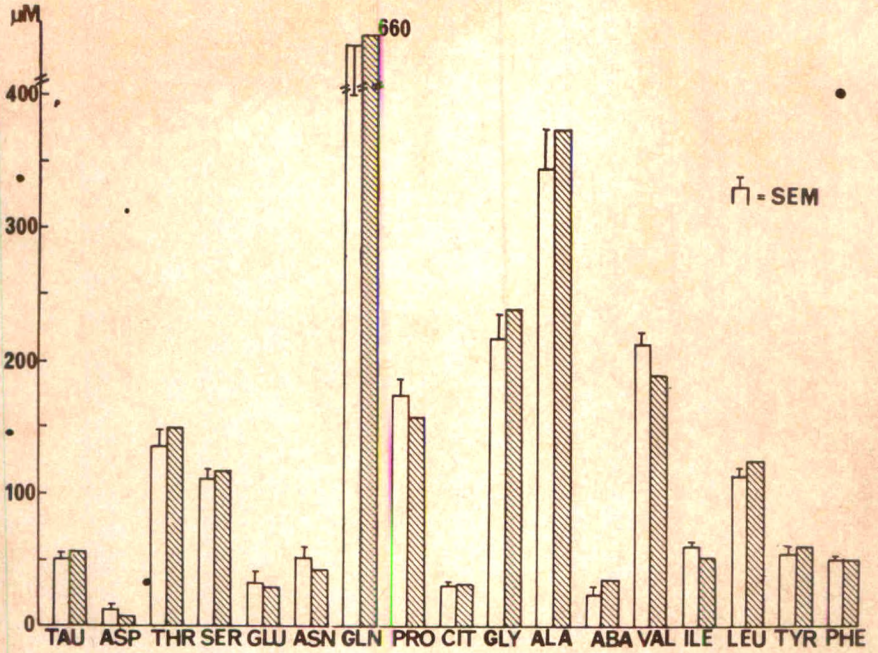
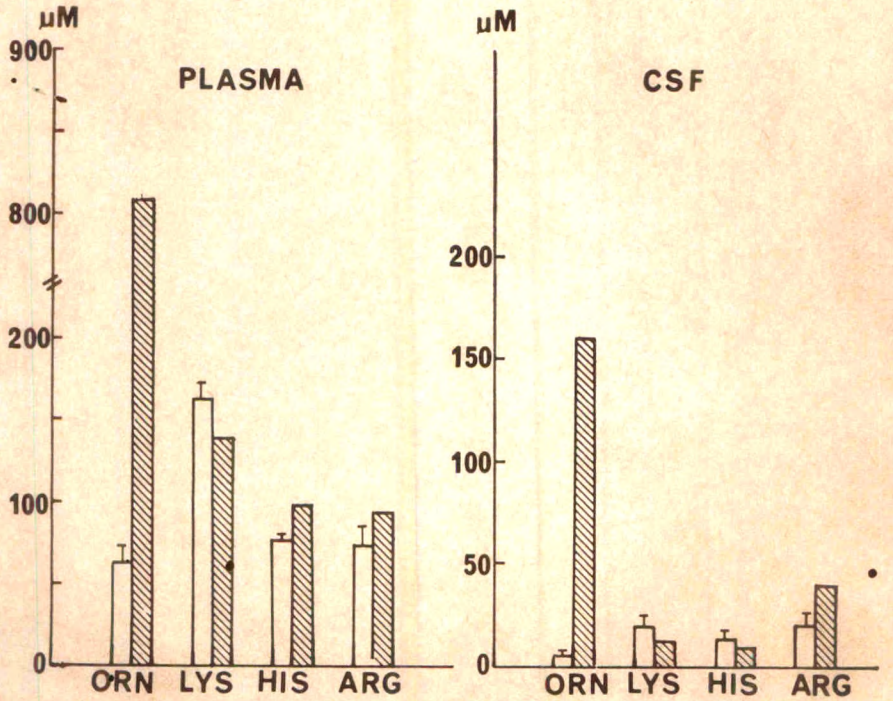


Fig. 10 (McCulloch and Marliss). Normal levels ± SEM in ten normal adults (open bars) of plasma acidic and neutral amino acids compared with the values in our patient (shaded bars). TAU indicates taurine; ASP, aspartic acid; THR, threonine; SER, serine; GLU, glutamic acid; ASN, asparagine; GLN, glutamine; PRO, proline; CIT, citrulline; GLY, glycine; ALA, alanine; ABA, alpha-amino-n-butyric acid; VAL, valine; ILE, isoleucine; LEU, leucine; TYR, tyrosine; and PHE, phenylalanine.



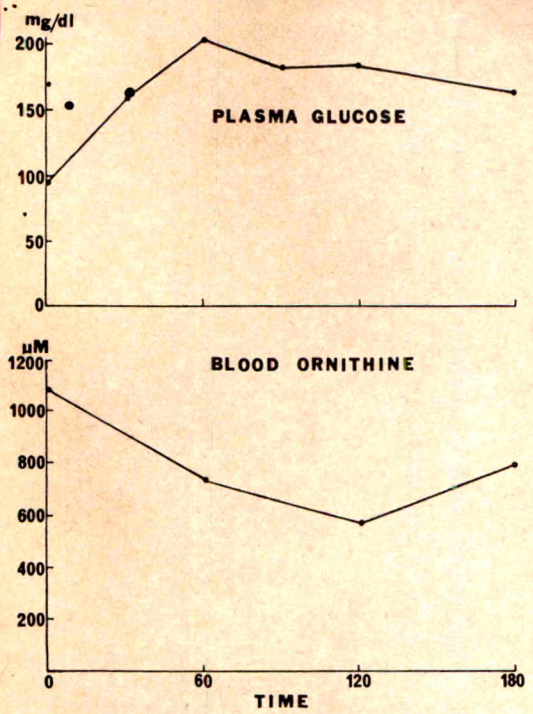


Fig. 12 (McCulloch and Marliss). Glucose tolerance test showing rise of plasma glucose to 200 mg/dl with slow return and decline of ornithine levels during provoked hyperglycemia.

venous plasma from all four first-degree relatives; all showed ornithine levels and normal levels for the other amino acids.

Discussion

This patient shows the picture of gyrate atrophy of the choroid and retina with hyperornithinemia, as described by Takki,[1] and Takki and Simell.[2] However, he reveals other changes which may well indicate a widespread metabolic defect of which the eyes are only one aspect: (1) gyrate atrophy of the choroid and retina; (2) cataracts; (3) hyperornithinemia with production of ornithine by muscles, splanchnic structures (liver, gut), and kidney; (4) abnormality of the nervous system—abnormal electroencephalogram and slow conduction by the optic nerve; (5) abnormal serum uric acid; (6) glucose intolerance; and (7) abnormal muscle with abnormal enzyme reaction and abnormal tubular aggregates within the fibers.

These abnormalities may all represent some aspect of the primary metabolic disease or, as the cataracts, may be a local response to some neighboring degeneration. However, until further evidence is available all of the changes should be considered as part of a generalized metabolic disturbance, in which the eye has been the only "target organ" hitherto recognized.

The greater than tenfold increase in circulating ornithine is similar to that previously reported.[1] In contrast to the re-

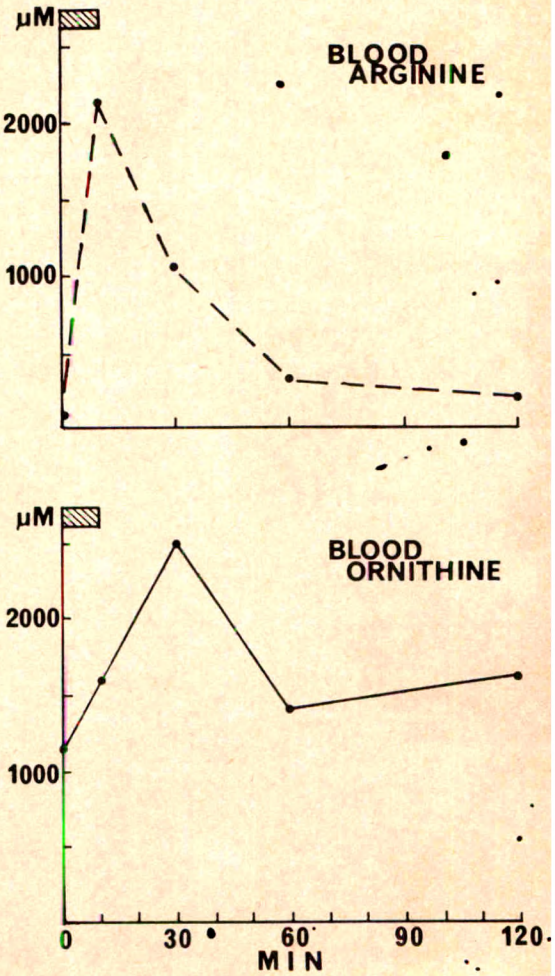


Fig. 13 (McCulloch and Marliss). Arginine infusion test showing rise of ornithine on infusing arginine.

markably large series reported,[1,2] there is no history of other cases in the family. However, the provocative test of ornithine loading[2] has not been performed. Hence, the inheritance in this instance is presumptive, and is either recessive or represents a mutant.

The present study demonstrates that the disease is not restricted to the eyes. The total extent of tissues involved cannot be determined, but is certainly broad enough to suggest a systemic metabolic derangement. This report shows that a substance behaving identically to ornithine in the assay system is produced by muscle, kidney, and the spanchnic bed. It further documents a nonspecific, though marked, anatomic lesion in the muscle that goes along with the metabolic abnormality demonstrated. The ultrastructural tubular aggregates shown in the patient have previously been associated with a variety of conditions manifesting muscle dysfunction[3]; they appear to be nonspecific as to cause. The significance of the abnormal electroencephalogram is also speculative, but must be interpreted in the light of the high cerebrospinal fluid ornithine observed. Such abnormalities have been found previously.[1]

A schema of the known metabolic pathways in which ornithine participates is shown in Figure 15. It is unlikely that a disorder of the urea cycle is present, as these present clinically early in life with serious neurologic disorders, and inability to properly dispose of ammonia, and do not necessarily display hyperornithinemia.[7] The relatively normal levels of other reactants of the urea cycle that have been measured would support this inference. Takki and his colleagues have implicated ornithine-ketoacid transaminase as the site of the defect,[1] and whereas this has been reported to occur in other circumstances,[8] the data in gyrate atrophy have not been published. In general, transaminase enzymes are rarely if ever rate-limiting; but this is a most unusual one, and could possibly be a major site of regulation of ornithine catabolism or production.[9]

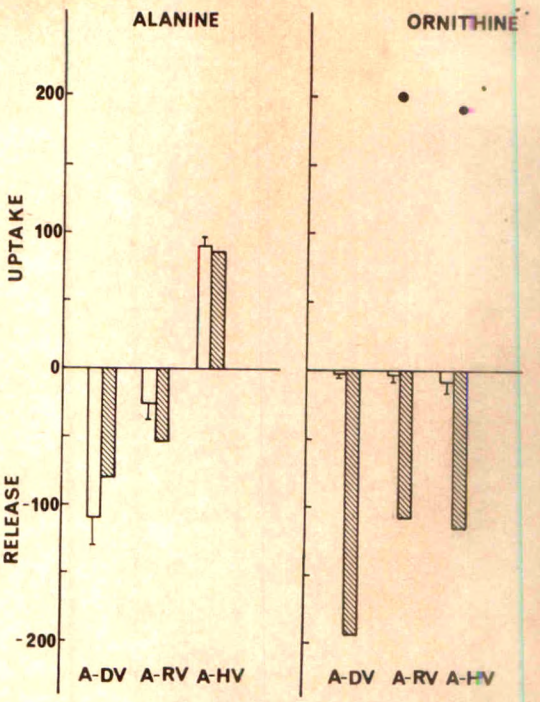


Fig. 14 (McCulloch and Marliss). Arteriovenous differences of plasma amino acids. A-DV designates artery to vein in deep forearm; A-RV, artery to renal vein; A-HV, artery to hepatic vein; normal (open bars), our patient (shaded bars). Ornithine is released by muscle, kidney, and splanchnic area.

The enzyme regulating interconversion of glutamine-γ-semialdehyde to glutamic acid, a dehydrogenase, would be another possible step responsible for accumulation of ornithine. It is unlikely that steps in the biosynthesis of proline are at fault, since all aspects of proline metabolism were normal in the present case and in those reported previously.[1]

Ornithine is a product in the reaction sequence leading from arginine (a transaminidase with glycine) and leading to creatine synthesis. If there were a block in this pathway, the ornithine produced would originate from arginine, which would have to be either synthesized in the tissues involved, or taken up by them. In light of the output of arginine from muscle in the present case, and of the normal levels of creatine in the circulation (not shown), an abnor-

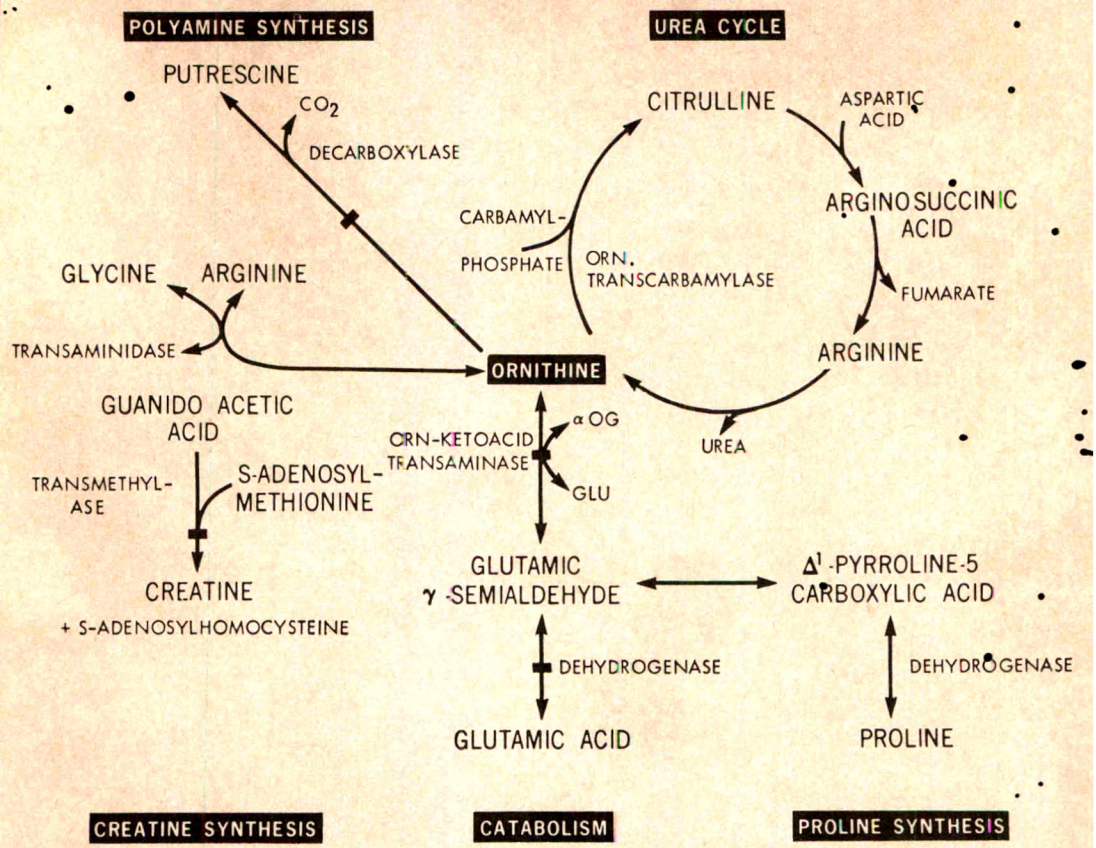


Fig. 15 (McCulloch and Marliss). Chart of metabolic systems that involve ornithine.

mality in this pathway is considered to be exceedingly unlikely.

Ornithine is the reactant which, by decarboxylation, yields putrescine, one of the essential polyamines. There are no data bearing on whether this pathway may contribute to the observed hyperornithinemia. Other than those shown and discussed, more remote pathways that impinge on intermediates of ornithine metabolism could also be implicated.

The critical question in relation to the ocular involvement is whether it is directly caused by the high levels of ornithine, or whether it is a reflection of the lens and choroid being unusually susceptible to a primary defect, of which a concomitant happens to involve ornithine metabolism. This question has been reviewed,[2] but remains unresolved. Two patients with a threefold to fourfold elevation of ornithine had normal fundi,[10] and the same applies to six cases with similar hyperornithinemia, due to decreased carbamyl phosphate synthetase activity.[11] Since ornithine is an intermediate of so many critical pathways, it could well be that the abnormality seen, though marked, is the tip of a metabolic "iceberg." The finding in this study and the enzymatic studies underway on fibroblasts and muscle tissue from this patient may throw further light on the site of the biochemical derangement. Moreover, simple dietary maneuvers capable of inducing marked decreases in circulating ornithine levels suggest that an appropriate treatment might be devised which would achieve control over the progressive nature of the disease.

Summary

A case of gyrate atrophy of the choroid and retina and hyperornithinemia in a 28-year-old man was subjected to extensive clinical and biochemical investigation. The familial occurrence of the ocular disease and of abnormality of amino acids was unique to this patient, being absent in parents and siblings. He presented with progressive visual loss, and had cataracts and large areas of peripheral lacunar atrophy. Clinically there was no other abnormality. However, he was hyperuricemic and had an abnormal electroencephalogram. Despite otherwise normal biochemical indices of hepatic, renal, and muscle function, selective catheterization of an artery, the hepatic vein, the renal vein, and a deep forearm vein showed all of these circulatory beds to be producing ornithine according to arteriovenous difference measurements. Cerebrospinal fluid and urine contained increased amounts of ornithine. Though electromyography was normal a muscle biopsy specimen was abnormal. Clinical tests including arginine loading, glucose tolerance testing, and other measurements of blood variables provided inferences as to the metabolic locus of the abnormality. The syndrome is a systemic multiorgan disorder in which the choroid and retina would appear to be target organs and the hyperornithinemia to be of as yet undetermined cause and pathogenic significance.

Acknowledgments

M. L. Halperin, M.D., G. Scrimgeour, Ph.D., R. P. Humphreys, M.D., and N. B. Rewcastle, M.D., supplied diagnostic procedures, discussion and review of pathological, clinical, and biochemical aspects of the study. N. L. Bailey, M.D., supplied clinical data on one of the sisters.

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HISTOLOGIC LOCALIZATION OF SODIUM FLUORESCEIN IN HUMAN OCULAR TISSUES

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Washington, D.C.

In 1961, Novotny and Alvis[1] first introduced the technique of fluorescein angiography. With this technique, clinicians were able to study the dynamics of ocular circulation. The histologic localization of fluorescein by means of fluorescence microscopy has not been possible with conventional histologic techniques because sodium fluorescein is soluble in both aqueous and alcoholic media.

In 1970, Machemer[2] tried to overcome this difficulty by using a fluorescein dye tagged to albumin. He was able to provide, for the first time, histopathologic interpretation of an ocular angiogram in the owl monkey. Since the molecular weight of the albumin tagged by a fluorescent dye was significantly greater than that of sodium fluorescein, there may have been leakage of fluorescein at certain anatomic sites that would not permit passage of the tagged albumin molecule.

In 1971, Grayson and Laties[3] demonstrated that unconjugated sodium fluorescein could be localized in freeze-dried microscopic sections of eyes of rhesus and squirrel monkeys and rabbits.

We observed the distribution pattern and demonstrated the barriers to diffusion of unconjugated sodium fluorescein in normal human ocular tissues.

From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology, and the Department of Ophthalmology, George Washington University Medical Center (Dr. Tso), Washington, D.C. This study was supported in part by Public Health Service research grant EY-00790, and training grant EY-00032 from the National Eye Institute.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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MATERIAL AND METHOD

Eight eyes were obtained from seven patients with intraocular malignant melanomas and one patient with total glaucoma. Two to 20 minutes before surgical transection of the optic nerve of the enucleated globe, 5 ml of 10% sodium fluorescein was injected intravenously. Upon enucleation, the globe was quickly frozen in a container of isopentane cooled in a liquid nitrogen bath. A temperature of −160° was attained and then slowly elevated to −20°C, at which time the globe was then cut into four to six pieces with a razor blade. The tissue was freeze-dried at −35°C for one to three weeks and embedded in paraffin without the use of intermediate solvents. Sections 5 to 15 μ thick were cut on a rotating microtome and coverslipped, with xylene as the mounting medium. Normal human eyes without in vivo injection of sodium fluorescein were obtained at autopsy for comparison and were processed in an identical fashion. The specimens were photographed with a Zeiss photomicroscope equipped for fluorescence with a BG-12 excitation filter and Zeiss 47 barrier filter and high-speed Ektachrome film. Paired photographs were taken of similar areas in the experimental and control eyes with identical exposure times.

RESULTS

Fluorescein was layered on the external surface of the corneal epithelium. In the corneal stroma, fluorescein staining was most intense at the corneoscleral limbus, with decreasing intensity toward the center.

The iris did not demonstrate extravascular fluorescein in eyes taken during the first five minutes after injection of fluorescein, but staining was observed in the anterior border tissue (Fig. 1, top). After 15 minutes, fluorescein was present diffusely

throughout the stroma and extended to the dilator muscles (Fig. 1, bottom).

Two minutes after injection of fluorescein, diffuse staining was observed in the stroma of the ciliary body, but only a minimal amount of fluorescein staining was observed in the basement membrane of the nonpigmented ciliary epithelium (Fig. 2, top). A specimen obtained after four minutes showed more intense fluorescence in the basement membrane of the nonpigmented epithelium (Fig. 2, bottom). With increasing time, the vessel walls and perivascular tissues of larger vessels of the ciliary body exhibited progressive staining and increased diffusion of fluorescein.

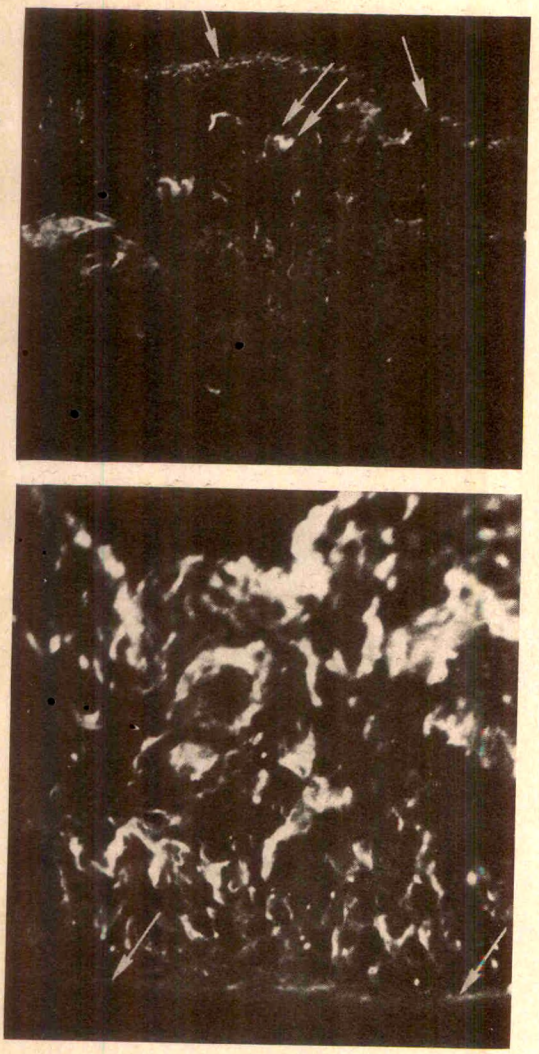


Fig. 1 (McMahon, Tso, and McLean). Top, Iris four minutes after injection of fluorescein. Blood vessels (double arrows) and anterior border layer of iris (single arrows) are fluorescing. Slight autofluorescence is observed in the stroma (AFIP Neg. 75-2099, ×40). Bottom, Iris 15 minutes after injection of fluorescein. Fluorescence is intense in the anterior border tissue and is diffuse in the stroma, extending to the anterior border of the dilator muscle (arrows) (AFIP Neg. 75-2100, ×63).

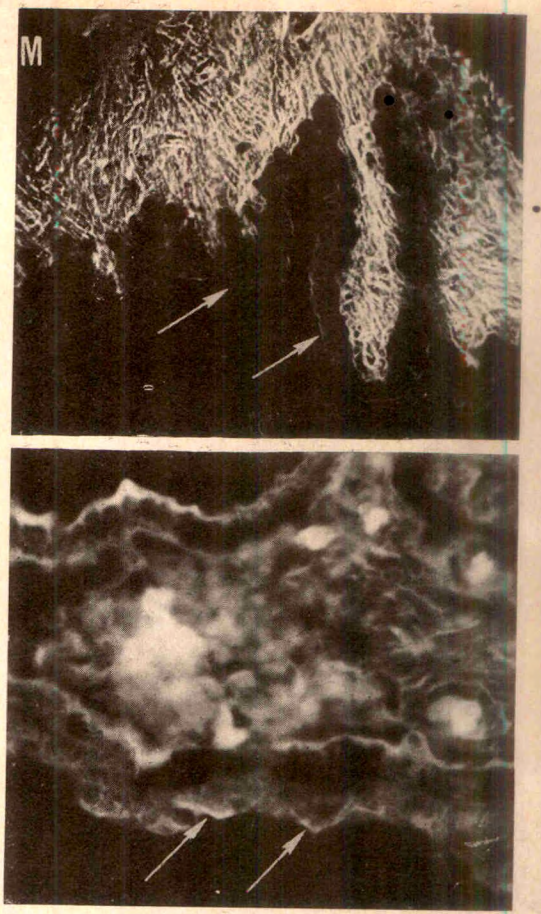


Fig. 2 (McMahon, Tso, and McLean). Top, Ciliary body two minutes after injection of fluorescein. The stroma fluoresces diffusely, but there is minimal fluorescence in the ciliary muscles (M) and in the basement membrane (arrows) of the nonpigmented ciliary epithelium (AFIP Neg. 75-2101, ×40). Bottom, Ciliary body four minutes after injection of fluorescein. The stromal collagen fluoresces diffusely, and fluorescein is also present in the basement membrane of the nonpigmented ciliary epithelium (arrows) (AFIP Neg. 75-2102, ×160).

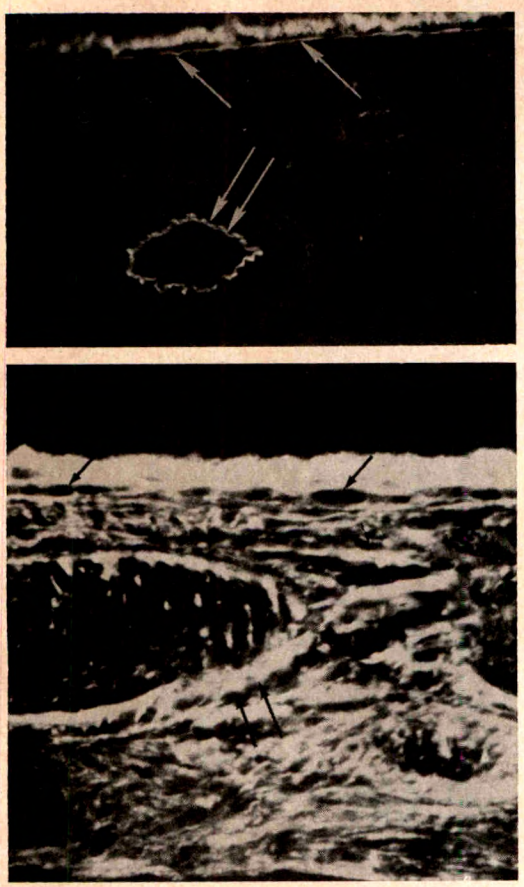


Fig. 3 (McMahon, Tso, and McLean). Top, Choroidal control. A section from an eye processed by the same freeze-drying technique but without prior injection of fluorescein. Autofluorescence is observed in the lipofuscin granules of the retinal pigment epithelium, in Bruch's membrane (single arrows), and in the internal elastic lamina of the artery (double arrows) (AFIP Neg. 75-2103, ×63). Bottom, Posterior choroid two minutes after injection of fluorescein. Fluorescein has diffused into the choroidal stroma; the most intense fluorescence is around the choriocapillaris (single arrows) and in the perivascular tissues (double arrows) (AFIP Neg. 75-2104, ×63).

At two minutes there was marked extravasation of dye in the choroid, external to the retinal pigment epithelium, but decreasing intensity of fluorescence was observed in the stroma of the outer choroid (Fig. 3, bottom), where only the larger choroidal vessels demonstrated perivascular fluorescence. In the control eyes, autofluorescence of Bruch's membrane, the internal elastic laminae of choroidal arteries, and lipofuscin granules in the retinal pigment epithelium were observed (Fig. 3, top). In the eyes obtained surgically after in vivo injection of sodium fluorescein, fluorescence was more intense and more diffuse in the region of Bruch's membrane than in the control eyes. There was maximum fluorescence in specimens obtained two minutes after injection. In specimens obtained after 15 to 20 minutes, fluorescence in Bruch's membrane was still considerably more intense than autofluorescence, while the fluorescence in the stroma of the choroid was faint and diffuse throughout its thickness. The sclera was also mildly stained. Drusen were observed in some of the specimens showing fluorescein staining of the drusenoid material, and autofluorescence of lipofuscin granules in the pigment epithelium overlying the drusen was also noted (Fig. 4).

Retinal vessels were partially filled with dye two minutes after fluorescein injection (Fig. 5). Minimal staining of the vessel walls was noted in the specimen obtained 20 minutes after injection. No fluorescein was found in the extravascular tissue in any section of normal retina. In the peripheral retina, areas of mild cystoid degeneration did not demonstrate extravasation of fluorescein. In an area of advanced cystoid degeneration, however, accumulation of dye along the inner retinal layers was noted (Fig. 6). In the region of the optic disk five minutes after injection, fluorescence was noted primarily within the intravascular spaces. There was moderate diffusion of fluorescein from the heavily stained border tissue of Elschnig into the peripheral nerve bundles. The sclera and episclera in the region of the circle of Zinn-Haller fluoresced intensely, but less intense fluorescence was noted in the lamina scleralis[4] of the optic nerve head (Fig. 7). At 20 minutes there was heavy fluorescence of the glial columns and minimal fluorescence in the nerve bundles at the level of the lamina choroidalis[4] of the optic nerve head. The border tissue of

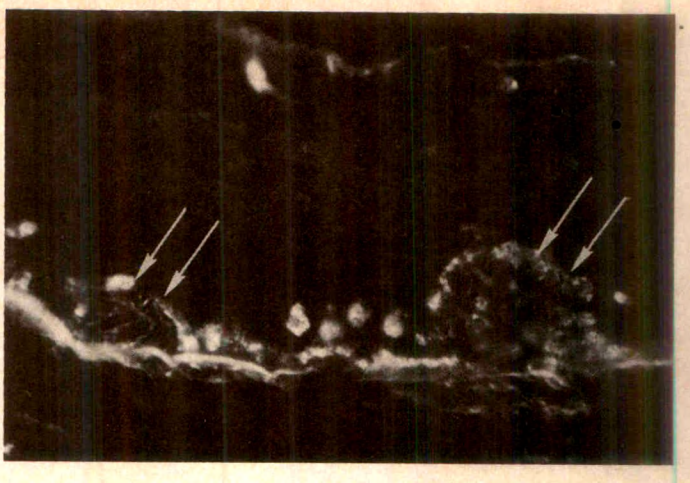


Fig. 4 (McMahon, Tso, and McLean). Drusen of Bruch's membrane. Fingers of fluorescence are noted projecting from Bruch's membrane toward the retinal pigment epithelium. Autofluorescence of lipofuscin in retinal pigment epithelium is observed (double arrows) (AFIP Neg. 75-2105, ×63).

Elschnig continued to show intense fluorescence (Fig. 8, top). The connective tissue at the lamina scleralis stained most heavily (Fig. 8, bottom). In the optic nerve immediately posterior to the lamina scleralis, most of the fluorescein was seen in the extravascular space in the septa of the optic nerve. In the orbital portion of the optic nerve, however, only intravascular fluorescein was observed (Fig. 9). The dura mater adjacent to the globe was examined and showed fluorescence.

Discussion

The localization of fluorescein in histologic sections is complicated by the solubility of fluorescein in aqueous and alcoholic media. In the conventional method of embedding, using formalin fixation and alcohol dehydration, fluorescein would diffuse throughout the tissues and would be extracted from the specimen. To overcome this difficulty, many investigators have tried various methods. One of the methods is the use of frozen sections. To prevent diffusion of fluorescein with this

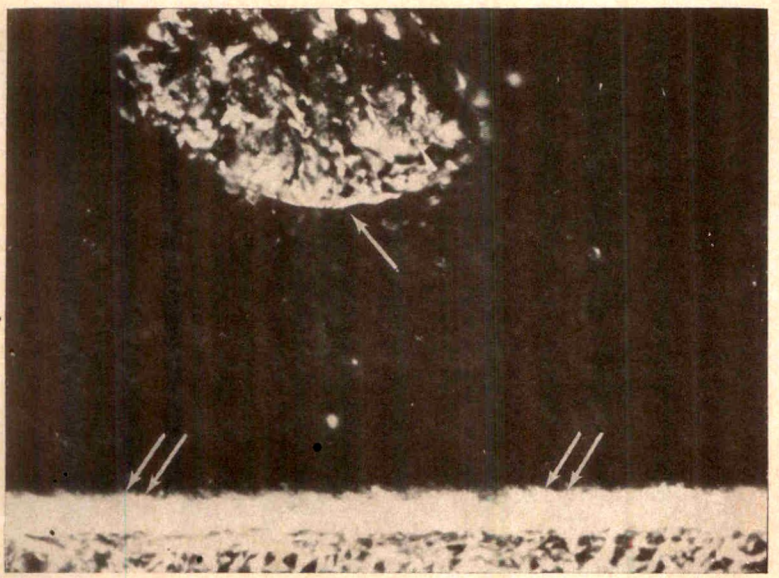


Fig. 5 (McMahon, Tso, and McLean). Normal retina. There is intravascular fluorescein (single arrow) without leakage. Autofluorescence is observed in the lipofuscin granules (double arrows) and in Bruch's membrane (AFIP Neg. 75-2989-1. ×63).

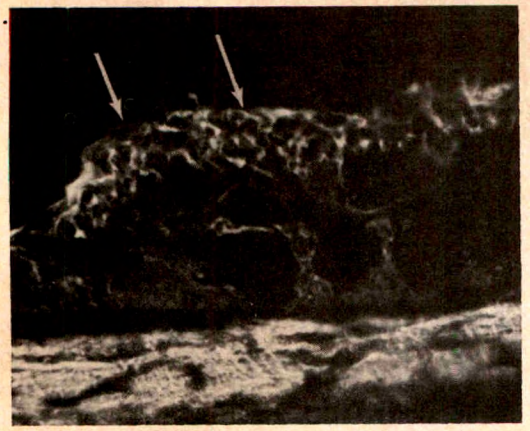


Fig. 6 (McMahon, Tso, and McLean). Peripheral cystoid degeneration of the retina. Fluorescence is observed in the inner layers (arrows) of the retina, which show marked cystoid degeneration. The inner choroid is also fluorescent (AFIP Neg. 74-2107, ×40).

technique, the sections must be cut at −35°C and must not be allowed to melt and air-dry.[5] Because of these difficulties we feel a better technique is to freeze-dry and embed in paraffin before sectioning. By this technique we consistently observed a completely dark background, while investigators using the frozen-section technique often had background fluorescence in their photomicrographs. A second problem in the localization of fluorescein in histologic sections is the differentiation of fluorescein fluorescence from tissue autofluorescence. To distinguish these two types of fluorescence we used matched photomicrographs of controls with exposure times identical to those of the experimental eyes. By this means we were able to determine the normal baseline autofluorescence. A further advantage was that the tinctorial difference of fluorescein fluorescence and autofluorescence facilitated interpretation.

Fluorescein angiography of the iris is currently gaining popularity as a diagnostic tool. The normal angiographic pattern consists of early intravascular retention of dye with a slow persistent staining of the stroma.[6] It has also been reported that the iris vessels have tight junctions.[7] Our results support these observations. In our specimens there was minimal stromal staining that occurred after the first five minutes. This staining was not localized around blood vessels but was noted mostly in the anterior border tissue of iris, suggesting that it probably represents absorption of dye from the aqueous humor.

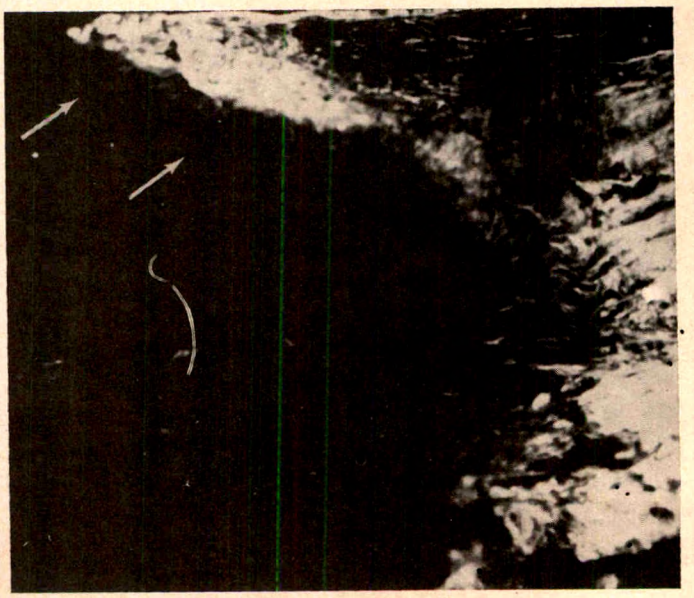


Fig. 7 (McMahon, Tso, and McLean). Normal optic disk five minutes after injection of fluorescein. The border tissue of Elschnig and sclera fluoresce intensely with diffusion of fluorescein into the adjacent optic nerve tissues (arrows) (AFIP Neg. 75-2989-2), ×40).

The ciliary body demonstrated fluorescein staining of the basement membrane of the nonpigmented epithelium. The presence of fluorescein in this region indicates that this substance passes through the ciliary epithelium in the formation of aqueous humor.

Our results also demonstrated the presence of the blood-retinal barrier. Diffusion was not observed either from the retinal vessels or across the retinal pigment epithelium from the choriocapillaris. This barrier is attributable to the zonula occludens present between the endothelial cells of the retinal vessels and the retinal pigment epithelial cells.[4] Our observations agree with those of Grayson, Tsukahara, and Laties[8] but differ from those of Mizuno, Sasaki, and Ohtsuki[9] who found leakage of dye across the pigment epithelium in the rat and possible leakage in the monkey. It is doubtful that the difference between rat and monkey observed by Mizuno, Sasaki, and Ohtsuki[9] is due to a variation between species, since a definite blood-retinal barrier has been demonstrated at the retinal pigment epithelium in experimental animals.[10]

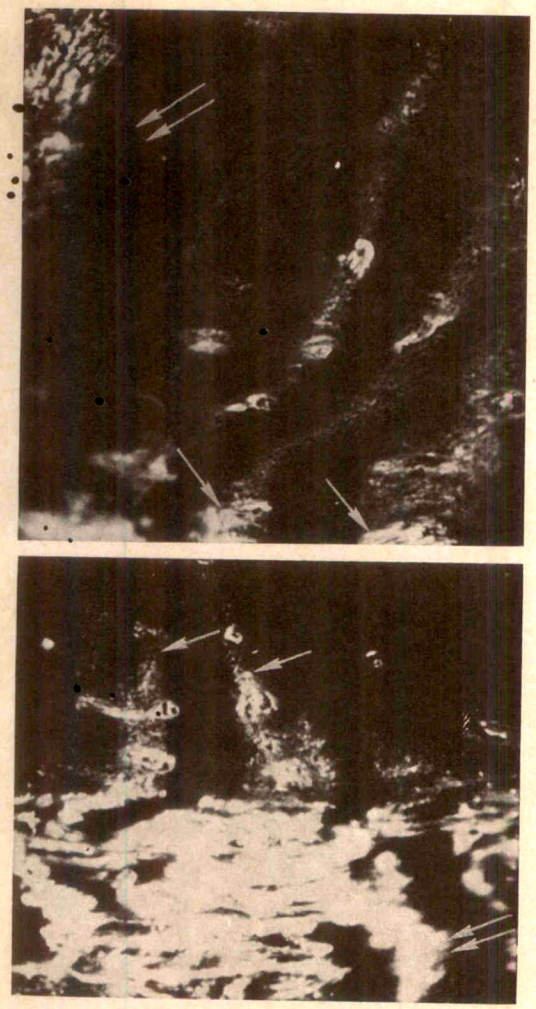


Fig. 8 (McMahon, Tso, and McLean). Top, Normal optic disk 20 minutes after injection of fluorescein. The lamina scleralis fluoresces intensely (single arrows). Extension of fluorescence in the glial columns is observed. There is minimal staining of the nerve adjacent to the border tissue of Elschnig (double arrows) (AFIP Neg. 75-2108, ×63). Bottom, The lamina scleralis stains intensely, and there is extension of fluorescein anteriorly into the glial columns (single arrows) and posteriorly into the optic nerve septa (double arrows) (AFIP Neg. 75-2109, ×40).

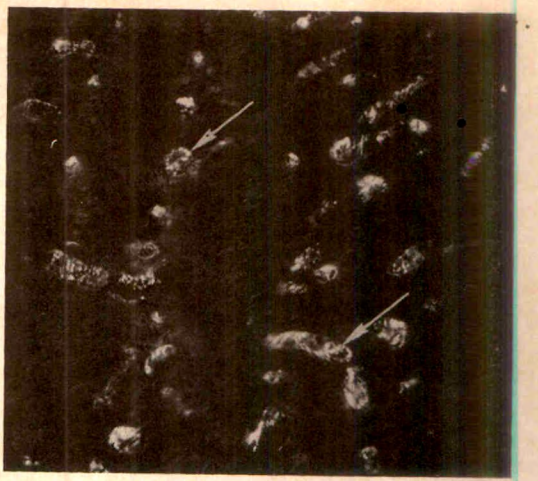


Fig. 9 (McMahon, Tso, and McLean). Optic nerve. The capillaries of the optic nerve demonstrate intravascular fluorescein (arrows) without leakage into the neural tissue (AFIP Neg. 75-2110, ×63).

Fluorescein was noted extravascularly in areas of advanced peripheral cystoid degeneration. Several mechanisms may explain this pattern. The blood-retinal barrier could be disrupted in these areas with the result that fluorescein diffuses from either the retinal vessels or the choroid. Alternatively, it has been observed that fluorescein passes from the vitreous body into the normal retina and is actively transported into the

vascular system,[11] and it is possible that the accumulation of fluorescein in areas of cystoid degeneration is due to failure of this transport system to remove fluorescein diffusion from the vitreous body.

Our observations about the choroid essentially confirmed clinical findings by other authors studying normal and albino patients.[12,13] In our two-minute specimens, which corresponded to the late venous phase of fluorescein angiography, the choriocapillaris and larger choroidal vessels were partially filled with fluorescein. At this time the background fluorescence of the fundus in fluorescein angiography corresponded to the staining of Bruch's membrane and the leakage of dye into the stroma of the inner one third of the choroid. At 20 minutes after fluorescein injection, mild staining of the entire thickness of the choroid accounted for the background fluorescence. Mild fluorescein fluorescence was also noted in the sclera by fluorescence microscopy, but due to the staining and pigmentation of the choroid, the role of this scleral staining in producing late background fluorescence in clinical angiography is uncertain.

The drusen present in our specimens show early staining that persisted in the 20-minute specimens. The staining was mainly in the basal layers of the drusen, with finger-like projections of fluorescence pointing toward the retinal pigment epithelial layer. This pattern of fluorescence coincided with the areas of intense staining with the PAS reaction, suggesting that the fluorescein is bound to the basement membrane component of the drusen. This concept is supported by Vassar and Culling,[14] who demonstrated that when fluorescein is used as a histologic stain it is bound to basement membrane and reticulin.

The staining of the glial and collagenous portion of the optic disk in our specimens accounts for the late fluorescence of the disk noted on fluorescein angiography. Machemer,[2] using rhodamine lissamine B tagged to albumin, found a similar distribution of staining; but there have been differing opinions concerning the cause of fluorescence of the disk at the late stage of fluorescein angiography. Grayson and Laties[3] felt that the diffusion of fluorescein into the optic nerve was an important cause of the disk fluorescence. Studying the disk region in rhesus monkeys up to two minutes after fluorescein injection, they emphasized both scleral and choroidal leakage into the disk region and found the most brilliant fluorescence in the optic disk adjacent to the choroid. In our early specimens, from two to five minutes after fluorescein injection, fluorescein seems to have diffused into the optic disk from the border tissue of Elschnig and sclera. This finding is identical to that of Grayson and Laties.[3] Studies using horseradish peroxidase as a tracer in rhesus monkeys in our laboratory[15] indicate that the peroxidase moves into the optic disk primarily from the border tissue of Elschnig at the level of lamina choroidalis and that there is also moderate diffusion at the level of lamina scleralis.

In the specimens obtained from five to 20 minutes after fluorescein injection, the most intense fluorescein staining was observed in the glial and connective tissue columns of the lamina choroidalis and scleralis, and we believe that the pooling of fluorescein in these tissues represents the major factor of late fluorescence of the optic disk seen in clinical angiography. The amount of fluorescein permeating the optic nerve bundles is small and, therefore, only a minor factor.

The optic nerve immediately posterior to the lamina cribrosa demonstrated both intravascular and extravascular fluorescein. The capillaries of the optic nerve in our specimens appeared impermeable to the fluorescein molecule. Tight junctions of the optic nerve vessels have been demonstrated, which have been presumed to be related to the blood-optic nerve barrier.[16,17] The optic nerve septa immediately posterior to the lamina scleralis were stained with fluores-

cein. Diffusion of the fluorescein from the lamina scleralis is the most probable cause of this septal staining. The dura mater fluoresced heavily.

Summary

We studied the distribution pattern of sodium fluorescein in human eyes microscopically. The ciliary body showed early and diffuse leakage, with staining of the basement membrane of the nonpigmented ciliary epithelium, indicating movement of fluorescein from the ciliary body into the aqueous humor. After five minutes the iris stroma stained with fluorescein, probably from the aqueous humor. The retinal vessels and retinal pigment epithelium were impermeable to fluorescein. Corresponding to the background fluorescence seen in fluorescein angiography, fluorescence was present in Bruch's membrane and in the stroma of the inner one third of the choroid. Drusen stained most intensely in areas of greatest PAS positivity. Early fluorescence of the optic disk was the result of intravascular perfusion of the dye. Minimal diffusion of fluorescein from the fenestrated choroidal vessels across the border tissue of Elschnig into the peripheral optic nerve bundles was observed. Late fluorescence of the optic disk was due mainly to fluorescein staining of the lamina scleralis and glial columns.

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XEROPHTHALMIA AND ANTERIOR-SEGMENT BLINDNESS AMONG PRESCHOOL-AGE CHILDREN IN EL SALVADOR

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Vitamin A deficiency is thought to be the most important cause of childhood blindness in many underdeveloped countries,[1-5] resulting in an estimated 100,000 new blindnesses and perhaps an equal number of deaths annually.[6] While these estimates are largely based on clinical impression, they have resulted in pilot or nationwide public health intervention programs in at least half-a-dozen countries.[7] The present countrywide prevalence survey indicated that vitamin A deficiency is probably the leading if not principal cause of acquired bilateral anterior-segment blindness among preschool-age children in El Salvador, but the magnitude of the problem is considerably less than originally anticipated.

Background—El Salvador is the smallest and most densely populated country in Central America with over 400 people per square mile, and an estimated 1970 population of 3.4 million.[8] Infant mortality is estimated at 63.4 per 1,000 live births.

The society is basically rural. Over 100,000 small farmers live on less than one hectare (2.47 acres) of land. According to government statistics, piped water supplies are accessible to only 23% of rural families, and less than 1% have sewage disposal facilities. Seventy-five percent of the rural homes are wattle or adobe construction, and few have electricity. Not surprisingly, gastroenteritis is reportedly the leading cause of morbidity and mortality, especially among the pediatric age groups.

Surveys by the Institute of Nutrition of Central America and Panama (INCAP) identified El Salvador as having the highest prevalence of hypovitaminosis A in Central America,[9] and a hospital-based study demonstrated 20% of children suffering from marasmus and 12% suffering from kwashiorkor had concomitant clinical (corneal) evidence of severe vitamin A deficiency.[10,11] Biannual mass distribution of vitamin A capsules was begun in April of 1973 as part of a countrywide vaccination campaign.

The small size of El Salvador (roughly 60 × 160 miles), accessibility of even the remotest areas, and apparent high prevalence of hypovitaminosis A made it an ideal country in which to carry out the present survey.

MATERIAL AND METHODS

A countrywide prevalence survey of children, ages 1 through 6 years, was conducted during October to December 1973. Fifty-nine sample sites were selected by a multistage stratified technique with representation proportional to size. The slum areas of the three major cities, San Salvador, Santa Ana, and San Miguel, comprised the "urban" sample sites. A review of hospital records supported the clinical impression that vitamin A deficiency was not a problem among the wealthier urban classes. Recently prepared maps listing every house in each of the sample sites were provided by the Asociacion Demografica Salvadorena.

The field team was composed of an ophthalmologist, three two-nurse teams, and a nurse supervisor. Each nurse team was assigned a specific sector of that day's sampl

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site. The nurses entered each house in their sector, compiled identifying and socioeconomic data on every eligible child in the household, and assembled all available children at a central point for the ophthamologist. He examined the anterior segment of each child's eyes with a handlight, flipped the eyelids where indicated, noted obvious abnormalities, and determined whether the clarity of the media was compatible with a visual acuity better or worse than 20/200. Special attention was paid to those lesions potentially related to active xerophthalmia (conjunctival wrinkling and xerosis, Bitot spots, corneal xerosis, and keratomalacia) and its healed sequelae (nebulae, leukomata, staphylomata, and phthisis bulbi) (Fig. 1).

With historical data provided by an older family member, usually the mother, the ophthalmologist attempted to assign causes to all old, healed corneal abnormalities. The major categories included infection (gross purulence), measles (characteristic rash), trauma (clear-cut history of injury at the time of onset of the corneal damage), congenital (noted at or shortly after birth in an otherwise white and quiet eye), hypovitaminosis A (none of the above in an otherwise white and quiet eye—children invariably severely malnourished).

The nurse-supervisor reviewed 20 to 40% of all forms in the field, checking the responses with the families actually studied. All data were recorded on precoded forms, transferred to 80-column IBM cards, and analyzed by sorter and computer.

Results

After four weeks of training and standardization, two of them in the field, the study got underway on Oct. 15 and was completed by late December 1973.

Sample—A total of 51 sample sites, of the initial 59, were visited (Fig. 2). One was omitted because it lay in a militarily restricted zone. The rest, the last sites to

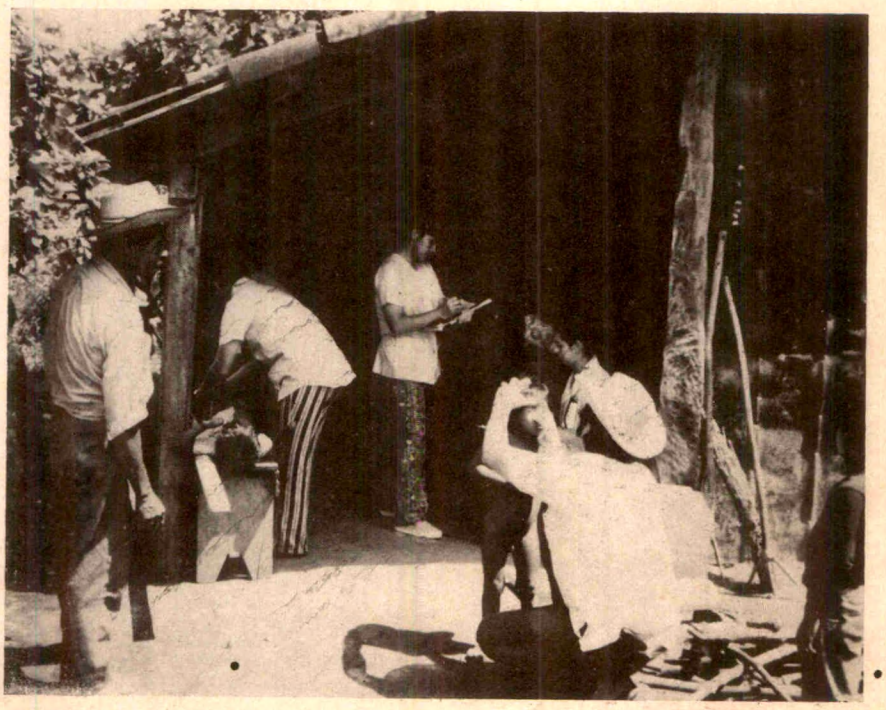


Fig. 1 (Sommer and associates). The field team working in rural El Salvador. The nurses are conducting interviews and collecting anthropometric measurements while the ophthalmologist is examining the anterior segment of each of the children's eyes.

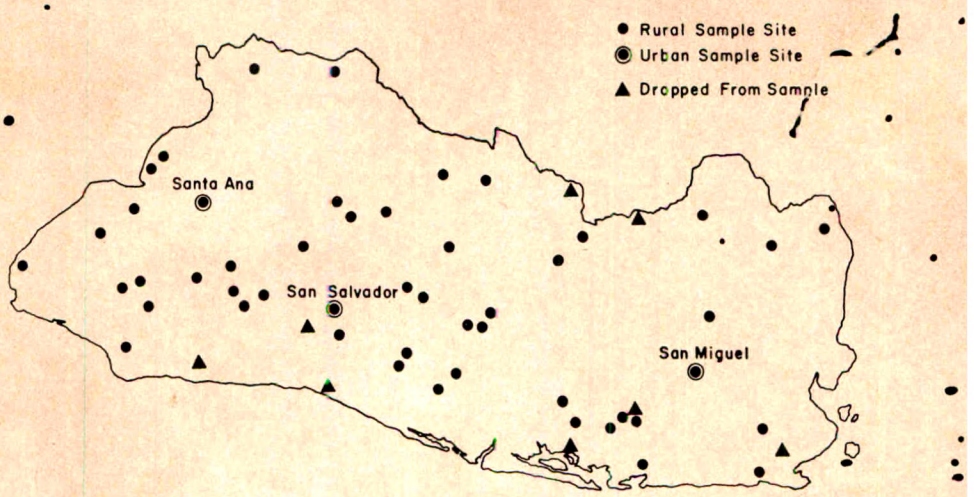


Fig. 2 (Sommer and associates). Map of El Salvador indicating the location of each of the selected sample sites, their urban/rural status, and whether or not they were actually studied.

be visited, had already received the second vitamin A distribution by mistake. Anticipating this possibility, these sites were randomly scattered across the country to prevent geographical bias.

A total of 9,014 houses were visited. Only 6,460 contained eligible children, of which 788 or 12% did not contribute to the sample. Two hundred ninety-eight of these families refused to cooperate, and 490 did not have any adult present. Thus, a total of 5,672 families were studied.

Sample families contained 9,743 eligible children. Two hundred thirty-five or 2.4% were listed but unavailable for examination. This represented 3.8% of urban and 1.7% of rural eligible children. There was little variation with age.

Age—The 9,508 children examined represent 1.2% of the estimated number of 1- to 6-year-olds in the entire country.[12] There was little variation with age, indicating lack of any significant sample bias (Table 1).

Sex—Through an oversight, the final field form omitted designation of sex. Instead, a systematic sample of forms of 100 families from the three urban sites, and 200 families from fifteen of the 48 rural sites was reviewed, and each child's sex was determined from his or her name. Overall, the number of boys and girls in this subsample was exactly equal (307:307). There was an insignificant differential between rural (223 male to 220 female) and urban (84 male to 87 female) samples.

Active signs of vitamin A deficiency—Only five children in the entire sample had Bitot spots, for a prevalence of 5.3 per

TABLE 1

CHILDREN EXAMINED

Geographic Zone	Age, yrs						Unknown	Total
	1	2	3	4	5	6		
Urban	518	532	500	505	529	517	25	3126
Rural	1078	1057	1118	982	1005	1072	70	6382
Total	1596	1589	1618	1487	1534	1589	95	9508

10,000 (Table 2). None of these children were under the age of 3, and three were 5 years or older. Four of these five children were from the rural sample, a representation twice that of the sample as a whole. The single urban child was from Santa Ana.

Conjunctival wrinkling was not considered a useful sign because of the lack of sharp definition. In no instance did it accompany other evidence of vitamin A deficiency or severe malnutrition. Four-tenths or 1% of the rural sample showed unusual degrees of wrinkling. None were under the age of 4 years. At age 4 years there was a sharp rise in prevalence to 1.2%, which persisted among older children.

No cases of active corneal involvement (xerosis or keratomalacia) were uncovered.

Healed corneal evidence of presumed vitamin A deficiency—Only three children in the entire sample had corneal damage thought to be secondary to vitamin A deficiency, for a prevalence of 3.2 per 10,000 children. The three children were 2, 4, and 6 years old, suggesting a cohort effect with the damage having occurred early in life, around age 2 years. The 6-year-old incurred his corneal damage at the age of 2 years, supporting the above conclusion. Age of onset in the 4-year-old was unknown.

TABLE 2

AGE DISTRIBUTION OF CHILDREN WITH OCULAR SIGNS OF VITAMIN A DEFICIENCY

Age, yrs	No. of Positive	
	Bitot Spots	Healed Corneal Lesions
1	—	—
2	—	1
3	2	—
4	—	1
5	1	—
6	2	1
Total	5	3
Prevalence per 10,000	5.3	3.2

TABLE 3

ESTIMATED IMPACT OF VITAMIN-A-RELATED CORNEAL DISEASE

	Mean	Confidence Limits (±2 Standard Deviations)
Prevalence of corneal disease	32/100 000	0–68/100 000
New surviving cases with involvement per year	43	0–90
New blindnesses per year	15	0–45

Two of these children had a unilateral adherent leukoma, and one had a staphyloma and adherent leukoma in one eye and an adherent leukoma and phthisis bulbi in the other eye. Each child was believed to have a visual acuity less than 20/200 in the involved eye. One of the children (the 2-year-old) had been seen and treated for keratomalacia at the Bloom Pediatric Hospital, the major facility in the country.

The oldest of the three was a boy, and the other two were girls. All three were from the rural sample.

Extent of the vitamin A problem—Table 3 depicts the estimated ocular impact of hypovitaminosis A in El Salvador. The prevalence of corneal disease was 32 per 100,000, which represents approximately 43 new surviving cases (of which 15 are bilaterally blind) per year. While the number of positive cases found in the survey is small,[3] the confidence limits provide a relatively accurate estimate (with 95% certainty) of the true magnitude of the problem.

Prevalence of corneal opacities—A total of 36 children had corneal opacities detectable with a handlight (Table 4). The majority, 56%, were secondary to trauma. Infection accounted for 17%, measles 11%, and presumed hypovitaminosis A, 8%. There was a strong association between both trauma and measles-induced lesions and

TABLE 4

CAUSES OF CORNEAL OPACITIES AMONG 1 TO 6-YEAR-OLDS

Cause	Cases	Percent of Total
Trauma	20	56
Infection	6	17
Measles	4	11
Hypovitaminosis A	3	8
Congenital	1	3
Unknown	2	6
Total	36	101

ban dwelling (Table 5). Children living in cities were at 19 times greater risk of acquiring a traumatic, and six times greater risk a measles-associated corneal lesion than their rural counterparts. These differences were statistically significant.

As would be expected, the prevalence of traumatic lesions increased with age. Among 4- to 6-year-olds it was more than twice that of 1- to 3-year-olds (282:125 per 100,000). Boys accounted for two thirds of the 18 cases for which the sex was noted. The prevalence of traumatic corneal lesions in the urban sample was 576 per 100,000, vs. only 31 per 100,000 in the rural sample.

Anterior-segment blindness—Fifteen children were felt to have anterior-segment acuity of less than 20/200 in one or both eyes. Approximately 50% of cases were secondary to trauma, measles, or vitamin A deficiency, with roughly equal representation

TABLE 5

RELATIVE RISKS OF CORNEAL OPACITIES—URBAN:RURAL

Cause	Cases U:R	Relative Risk U:R
Trauma	18:2	19:1*
Measles	3:1	6:1*
Infection	2:4	1:1
Hypovitaminosis A	0:3	0:1.5
Overall	27:9	6:1*

* $P < .05$

TABLE 6

CAUSES OF BILATERAL ANTERIOR SEGMENT BLINDNESS

Cause	Cases	Percent of Total
Measles	1	20
Hypovitaminosis A	1	20
Congenital leukomato	1	20
Congenital cataracts	2	40
Total	5	100

of each. One third had cataracts (four children), of which half (two) were congenital. There was one child with congenital and one with infectious corneal opacification, and one with congenital glaucoma. One third of the blindnesses were bilateral.

While trauma was responsible for the majority of corneal scars, it was not an important cause of bilateral anterior-segment blindness (Table 6). Only five of such cases were found: one each of measles, vitamin A deficiency, and congenital leukomata, and two with congenital cataracts. Vitamin A deficiency and measles, therefore, accounted for all the acquired bilateral anterior segment blindness in the small number of cases found. The prevalence of bilateral anterior segment blindness among these 1- to 6-year-olds was 5.3 per 10,000.

Conjunctivitis—Gross conjunctivitis was rampant; the vast majority purulent. In both the urban and rural samples 15.6% of the children were affected, 99.7% bilaterally. The highest prevalence was among the youngest age groups, 18% in 1- to 2½-year-olds. There was then a gradual decline to 13% in those 5½ years and older. There was no difference in prevalence by socioeconomic status.

DISCUSSION

Vitamin A deficiency might well be the most important cause of acquired bilateral anterior-segment blindness among the preschool-age population of El Salvador. Of

the two cases of acquired bilateral blindness found, we believed one was most compatible with healed keratomalacia on clinical and historic grounds. The other case of bilateral blindness was judged secondary to measles on the basis of a history of rash, the diagnosis allegedly assigned by the local hospital where the child was treated. His chart was subsequently found at the Bloom Hospital in the course of the retrospective study, however,[13] where it was noted he was transferred from the local hospital after nine days. On admission to Bloom a diagnosis of bilateral active keratomalacia was made, suggesting that this case was also secondary to hypovitaminosis A, exacerbated by the onset of measles.[14]

The prevalence of vitamin-A-related corneal disease was nonetheless far lower than anticipated and precluded its use in determining the effectiveness of the distribution program. There are roughly 43 new surviving cases and 15 new blindnesses per year in the entire country (excluding the controversial measles case*). It might be argued that the infrequency of Bitot spots was the result of the first vitamin A distribution six months earlier, but this would not explain the rarity of corneal scars. Additionally, only 80% of children actually received the capsule.[13] Even if the capsule were completely effective, and the "true" prevalence of Bitot spots five times our rate, it would still be less than 0.25% of 1- to 6-year-olds.

Previous estimates, based on chemical surveys and hospital reviews, were considerably higher. While part of this discrepancy may be temporally related, the other studies having preceded this one by seven to ten years, much is undoubtedly the result of differences in interpretation and technique. Chemical surveys can identify populations at risk of developing clinical disease, but they cannot predict the level of prevalence of such disease. Extrapolation from hospitalized patients is hazardous without knowing the proportion of patients who come to the hospital and the size of the reference population. The present study, on the other hand, is an unbiased sample survey of the entire population of 1- to 6-year-olds in the country.

Although the numbers are small, all three cases of presumed vitamin-A-related corneal disease, and four of five with Bitot spots, were rural. In contrast, almost all cases of traumatic corneal scars were urban, where the prevalence was 19 times that of the rural areas. Trauma is frequently listed as a major cause of blindness in underdeveloped countries.[4] In El Salvador it accounts for the majority of acquired corneal scars among preschoolers, but little if any bilateral blindness.

Sixteen percent of children had gross conjunctivitis, but it too was not an important cause of bilateral blindness. Sixty percent (three of five cases) of bilateral anterior segment blindness was congenital.

Estimates of the relative importance and magnitude of clinically significant vitamin A deficiency, and the potential benefit of vitamin A supplementation, require at a minimum, carefully conducted prevalence surveys. These should precede the institution of any intervention program.

Summary

A countrywide prevalence survey of 9,508 children was conducted in El Salvador to determine the prevalence of anterior-segment abnormalities and magnitude of clinical vitamin A deficiency. Thirty-six children had corneal opacities, 56% of them secondary to trauma. Such traumatic corneal opacities were 19 times more frequent among urban than rural children, 57.6 vs. 3.1 per 1,000. Keratomalacia accounted for only 8% of all corneal opacities, and for one (and possibly two) of the five cases of bilateral anterior-segment blindness encoun-

* Inclusion of this case would raise the estimated number of new annual surviving cases of corneal disease and bilateral blindness to 60 and 30, respectively.

tered. The prevalence of Bitot spots and vitamin-A-related corneal opacities was 5.3 and 3.2 per 10,000, respectively. There are an estimated 43 new surviving cases of vitamin-A-related corneal opacities in the country each year, one third of which result in bilateral blindness. Fifteen percent of all children examined had grossly purulent conjunctivitis.

ACKNOWLEDGMENTS

We thank Humberto Escapini, M.D., clinical consultant; Vilma deAparicio, M.D., and Luis Ochoa, M.D., for their advice and governmental coordination; and the teams of nurses who performed in the field, often under difficult conditions. We thank Querubina deParades, and the Asociacion Demografica Salvadorena; Julio Astacio, M.D., Minister of Health, government of El Salvador, and Susan T. Pettiss, M.D., director of Blindness Prevention, American Foundation for Overseas Blind.

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MASS DISTRIBUTION OF VITAMIN A AND THE PREVENTION OF KERATOMALACIA

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Because vitamin A deficiency is thought to be the leading cause of childhood blindness in many underdeveloped countries,[1-6] an expert group of the Pan American Health Organization officially recommended vitamin A supplementation of preschool-age populations.[7] India, Indonesia, Bangladesh, and the Philippines have already inaugurated pilot or nationwide distribution of massive doses of vitamin A.[8] There is no evidence, however, that such programs can effectively reduce the incidence of keratomalacia and other forms of vitamin-A-deficient corneal destruction. An assessment of the vitamin A distribution program in El Salvador suggests the opposite.

Background—Gastroenteritis is the leading cause of morbidity and mortality in El Salvador, especially in the pediatric age group. Serum surveys indicate it has the highest prevalence of hypovitaminosis A in Central America,[9] and a retrospective hospital chart review demonstrated that 20% of the children admitted with marasmus and 12% admitted with kwashiorkor had concomitant corneal evidence of severe vitamin A deficiency.[10-11]

Biannual mass distribution of vitamin A was begun in April 1973 as part of a well-publicized countrywide vaccination campaign. During April and May, and again in November and December, every child between the ages of 1 and 5 years present at the distribution center had the contents of a capsule of 200,000 international units of vitamin A and 40 international units of vitamin E squeezed into his mouth. Vigorous attempts were made to track down absent children. The principal members of the present study were in no way involved in either the design or execution of the distribution program.

MATERIAL AND METHODS

Records were reviewed of all children ages 1 to 9 years with selected discharge diagnoses from the Benjamin Bloom Children's Hospital in San Salvador, the capital. This modern 360-bed institution is the premier facility in the country, with wide geographic coverage. Its Ophthalmology Department is especially interested in the problems of hypovitaminosis A, and a preliminary survey indicated record retrieval was excellent.

All primary and secondary discharge diagnoses were coded on International Classification of Disease (ICD) specific index cards.[12] A specially trained nurse consulted this index and retrieved all charts with the following primary or secondary diagnosis: 260—hypovitaminosis A; 267—protein malnutrition; 268—marasmus; 269—malnutrition, type unspecified; 360—conjunctivitis; 371—corneal opacity; 378—other ocular disease; and 379—blindness.

These were felt to include the vast majority of keratomalacia cases. While some additional cases might have been missed, it was impractical to review every discharge from the hospital.

After filling out identifying information, height, weight, and measles history, the nurse passed the chart and its form to the ophthalmologist, who reviewed the clinical history and determined the child's [illegible] status, and whether or not it was compatible with active keratomalacia or corneal xerosis with ulceration. A second, "blind" re[illegible]

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TABLE 1

ACTIVE CASES OF VITAMIN-A-RELATED CORNEAL DISEASES

Clinical Description	No. of Cases		Total
	1972–1973	1973–1974	
Keratomalacia	18	14	32
Corneal ulcer	15	17	32
Total	33	31	64

for reproducibility indicated some shifting of morphologic diagnosis, but rarely the classification of active vitamin-A-related disease. All charts with any significant ocular pathology were reviewed a third time by the ophthalmologist and the principal investigator, and a final concensus was reached.

A three-year period was studied, April 1971 to March 1974. During the first year, however, the hospital was relocated, resulting in fluctuating numbers of beds and admission criteria, and the indexing changed, with a consequent loss of many charts. The results for 1971 through 1972 are therefore included in the descriptive data, but omitted from any comparisons of pre- and post-distribution periods. These were limited to the years immediately preceding and following inauguration of vitamin A distribution, April 1972 to March 1973 and April 1973 to March 1974, respectively.

RESULTS

The ICD files listed 3,713 charts with one or more of the selected diagnoses. Ninety-six percent (3,490) were retrieved. Approximately 280 charts mentioned some form of anterior-segment abnormality.

Criteria for severe, active hypovitaminosis-A-related corneal disease ("positive cases") included the clinical description of corneal ulcers, keratomalacia, or active perforation ascribed to hypovitaminosis A by the attending pediatrician or ophthalmic consultant, the latter taking precedence, and immediate treatment with massive doses of vitamin A.

Seventy-six cases met these criteria. In two additional instances, careful review failed to support the ophthalmologist's diagnosis of keratomalacia, and these were omitted. Eighty-four percent of the 75 positive cases had been examined by a member of the ophthalmology department, almost half of these by Dr. Escapini, professor and head of ophthalmology, and the clinical consultant to this study.

No. of cases—There was essentially no difference in the number of positive cases admitted in 1972 to 1973 and 1973 to 1974 (Table 1).

Omitting those patients too young or too old to have received the distributed vitamin leaves the results unchanged (Table 2).

Age—During the three-year period, patients with positive cases ranged in age from 2 months to 9 years. One third of all patients were under 1 year of age, and half of these were less than 6 months old. Almost two thirds of all patients (58%) were less than 2 years old. The age distribution during 1972 to 1973 was identical to that of the following year. Even 1971 to 1972, with its fewer cases, closely approximated these latter years (Table 3). The age distribution for the two clinical disease forms, corneal ulcers and keratomalacia, was similar.

Half of all the patients would have been less than 1 or more than 5 years of age at the time of the biannual distribution immediately preceding the onset of their corneal

TABLE 2

ADJUSTED* CASES OF ACTIVE CORNEAL DISEASE

Clinical Description	No. of Cases		Total
	1972–1973	1973–1974	
Keratomalacia	8	7	15
Corneal ulcer	9	7	16
Total	17	14	31

* Omitted were those children ineligible for participation in the distribution immediately preceding onset of their disease.

TABLE 3

AGE DISTRIBUTION OF ACTIVE CASES OF VITAMIN-A-RELATED CORNEAL DISEASE

Age, yrs	1971–1972		1972–1973		1973–1974	
	No.*	%†	No.	%	No.	%
0	3	25	11	33	10	32
1	3	25	9	27	8	26
2	1	8	3	9	3	10
3	3	25	5	15	3	10
4	1	8	2	6	1	3
5	—	—	—	—	1	3
≥6	1	8	3	9	5	16
Total	12	99	33	99	31	100

* Number of cases.
† Percent of annual total.

disease, and hence ineligible to receive the vitamin. Almost four fifths of these would have been too young (less than 1 year of age). This limited the maximum potential effectiveness of the program to 50% (Table 4).

Sex—Boys comprised almost two thirds of the 76 cases (62%), while girls contributed two thirds of the deaths (67%). The age distribution of male and female cases was identical.

Malnutrition—Clinically, 93% of the 3,490 children surveyed were severely malnourished (Grade 3 or worse). It was not possible, retrospectively, to divide these into kwashiorkor and marasmic types.

Every patient with presumed vitamin-A-related corneal disease suffered severe, concomitant malnutrition. Since fluctuations in the number or age distribution of patients admitted with malnutrition might conceivably influence the number of patients with corneal disease, independent of the availability of vitamin A, the proportion of malnourished patients with concomitant corneal disease is probably a better index of the effect of the intervention program (Table 5).

Overall and age-specific rates of vitamin-A-related corneal disease among malnourished patients were identical for the two years straddling the onset of distribution, 1972 to 1973 and 1973 to 1974, respectively. In each of the three years of study, the highest age-specific rates of corneal disease occurred in the fourth year of life.

TABLE 4

ELIGIBILITY OF PATIENTS FOR RECEIPT OF VITAMIN A*

	No.	% of Total
Ineligible		
<1 year old	28	37
>5 years old	6	11
Total	36	48
Eligible		
Total (ages 1–4)	40	52
Total	76	100

* At the distribution that would have immediately preceded the onset of corneal disease.

TABLE 5

ACTIVE CORNEAL DISEASE AMONG CHILDREN WITH SEVERE MALNUTRITION*

Age, yrs	1972–1973		1973–1974	
	Cases	Rate/1000	Cases	Rate/1000
0	11	29	10	27
1	9	27	8	24
2	3	20	3	20
3	5	53	3	31
4	2	22	1	14
≥5	3	15	6	30
Total	33	26	31	25

* Includes only children of known age, 98% of the total.

TABLE 6

MEASLES HISTORY AMONG CHILDREN WITH SEVERE MALNUTRITION*

Measles History	1971–1972		1972–1973		1973–1974		Total	
	A	B	A	B	A	B	A	B
No.	1	10	6	90	2	9	9	109
Percent of admissions	8.3	1.4	18.2	7.3	6.5	0.7	11.8	3.4

* A, with vitamin-A-related corneal disease; B, without apparent vitamin-A-related corneal disease.

Measles—All charts were reviewed for a history of recent measles (within one month of admission). When present, the family had invariably indicated it had caused a marked worsening of the patient's condition, and assumed it was responsible for the child's acute decompensation and eventual admission.

During the only full year before measles vaccination, 1972 to 1973, over twice as many children with corneal involvement than without had given a history of recent measles. A similar trend was apparent for each of the other two years. Because of the small number of cases, however, the difference is not statistically significant (Table 6).

The lowest age-specific prevalence of recent measles history among preschoolers was during the first year of life: only one of 24 children with corneal involvement. The last case of measles, regardless of corneal involvement, was admitted in June of 1974, one month after completion of the measles vaccination campaign.

Mortality—Eleven percent of all severely malnourished patients in the study died (Table 7). Mortality among those with corneal involvement was almost 50% higher ($P < .001$), entirely the result of an increased risk among girls. Mortality among boys with corneal involvement was essentially the same as among boys and girls with normal corneas.

Seasonality—Admissions for measles, malnutrition, and vitamin-A-related corneal disease are plotted in Figure 1. As already indicated, at least some of the change from 1971 to 1972 is artifactual.

Where curves are constructed from small numbers of admissions, as in the present instance of measles and corneal disease, they are apt to be erratic. These should be visually smoothed, with an emphasis on suggestive trends rather than absolute monthly peaks and dips.

In general, malnourished patients with and without corneal disease followed a similar seasonal course. The corneal disease curve appears unaltered in the immediate period after vitamin A distribution, April to June 1973. Adjustment for patients ineligible for participation because of age did not alter the results.

Over the three-year period, almost three-fourths (73%) of all vitamin-A-related corneal disease admissions occurred in the six-month period extending from May through October (Figure 2).

Region—Geographical representation was

TABLE 7

MORTALITY AMONG CHILDREN WITH SEVERE MALNUTRITION

Age, yrs	Cornea Normal		Cornea Involved	
	Deaths	Rate/100	Deaths	Rate/100
0–1	250	14	9	20
2–3	54	9	2	11
≥4	44	6	1	8
Total	360*	11†	12	16†
Sex				
Male	172	10	4	9‡
Female	188	12	8	28‡

* Includes 12 deaths of unknown age.
† Normal cornea: involved cornea $P < .001$.
‡ Corneal involvement—male:female $P < .05$.

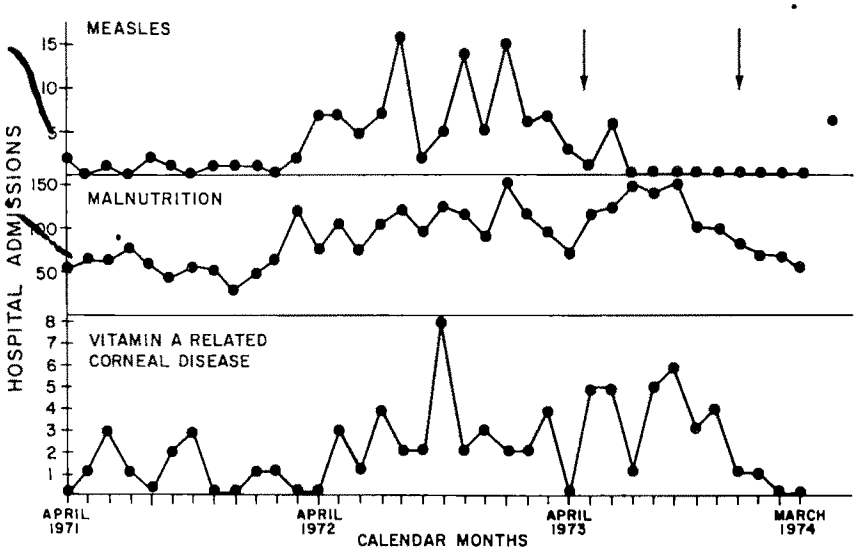


Fig. 1 (Sommer, Faich, and Quesada). Date of admission to the Benjamin Bloom Pediatric Hospital, El Salvador, of all patients in the study found to have had vitamin-A-related corneal disease, Grade 3 malnutrition, or a recent history of measles. The arrows indicate countrywide vitamin A distribution and measles vaccination (April to May 1973), and vitamin A distribution alone (December 1973).

wide. Nearly one third of all positive cases came from the metropolitan region, in which the hospital is located. Almost an equal proportion came from each of the adjoining regions. Only the two outlying regions contributed a disproportionately small number of cases.

Over 90% of all positive cases came from the rural areas, which contain 60% of the population.

Discussion

At least three factors appear to have contributed to the program's failure to reduce the number of hospital admissions with vitamin-A-related corneal abnormalities: the age distribution of active cases, the practical limitations of mass distribution, and the potential ineffectiveness of periodic mass dosage in children with severe persistent malnutrition. The first factor may be peculiar to El Salvador, but the latter two represent fundamental weaknesses in this approach.

Vitamin A distribution was limited to 1- to 4-year-olds, who were commonly assumed to contribute the vast majority of cases.[13] We were therefore surprised to find that one third of our patients were under 1, and 12%

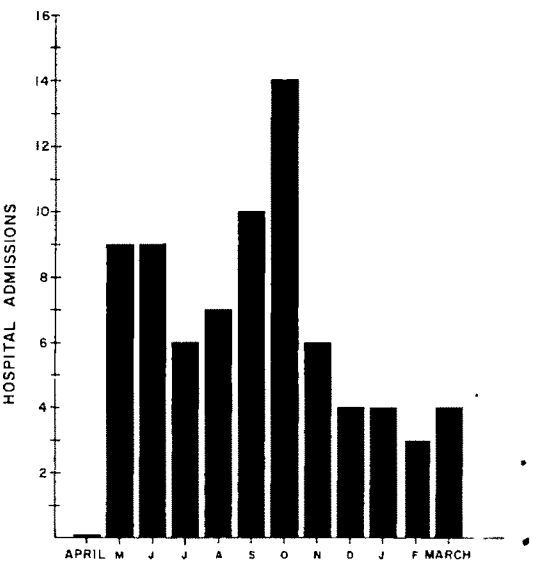


Fig. 2 (Sommer, Faich, and Quesada). Vitamin-A-related corneal disease among patients in the study by month of admission to the Benjamin Bloom Pediatric Hospital, El Salvador, accumulated over the three-year period, April 1971 to March 1974.

were 6 years or older. Half of all patients would have been ineligible to receive the vitamin A capsule at the distribution immediately preceding the onset of their disease. The program was therefore limited to a maximal potential effectiveness of only 50% before it was even instituted.

The large proportion of neonates may not be as unique as it appears. Other studies, especially in the older literature, had similar results.[14] The differences are probably culturally related: where breast feeding is abandoned earlier in life, and the severely malnourished young brought to the hospitals, a larger proportion of patients will be under 1 year old. This age distribution precludes an effective program: toxic reactions to 200,000 international units are common under the age of 1 year and while not serious, they are sure to limit the community's participation in the program.

Even when adjusted for these ineligible children, however, the program still proved ineffective. No mass distribution program ever reaches 100% of the target population, even one as carefully organized and vigorously pursued as El Salvador's. Measles serologic surveys before and after the initial campaign, which combined measles vaccination with vitamin A administration, demonstrate that at best 80% of eligible children were reached.[15] Those missed are likely to have been the ones at greatest risk.[16]

We were unable to determine whether any of the children with active disease or their sex and age matched controls had actually received the vitamin A capsule. Conceivably, all the cases could have come from among the 20% of 1- to 4-year-olds who never received the vitamin, although it is far more likely that some if not most represent frank prophylactic failures.

Because annual oral administration of 300,000 international units of vitamin A or biannual administration of 200,000 international units results in an elevation of mean serum vitamin A levels and a reduction in the prevalence of mild conjunctival evidence of clinical disease,[17-20] it has been assumed that mass distribution would prevent vitamin-A-related corneal destruction. As in the present study, however, corneal destruction is usually accompanied by severe generalized malnutrition,[1,10,21-24] which interferes with both the absorption and utilization of vitamin A.[25,26] Since normally nourished children absorb only 50% of this massive dose,[27] severely malnourished children might be expected to absorb even less. With the vitamin storage even lower to begin with, this dose, massive as it is, may provide inadequate protection. At least two children with uniocular keratomalacia went on to lose their second eye despite massive, daily, parenteral and oral therapy with vitamin A.

The relationship between corneal destruction and the variables of sex and measles remains unclear. While boys contributed two thirds of the cases, mortality among girls was four times as high, suggesting that only the sickest girls were brought in, a bias in hospitalization rates that precludes any definitive statement about relative risks of disease in the community at large. Absence of an increased mortality among boys with corneal involvement suggests that vitamin A deficiency, per se, was not responsible for the high death rate among these girls.

A recent history of measles was variably but consistently more common among children with vitamin-A-related corneal destruction than among malnourished patients as a whole. The dramatic reduction in measles cases following mass vaccination, however, had little if any impact on the occurrence of active corneal disease. It is therefore unlikely that measles is an important predisposing factor to vitamin-A-related corneal disease in El Salvador, or that significant numbers of measles keratitis cases were misdiagnosed as vitamin A deficiency. The contrast between the results of measles vaccination and vitamin A administration, performed at the same time, is striking: measles disappeared, while vitamin-A-related corneal destruction followed its usual

seasonal course. Lack of concrete evidence that mass distribution can prevent vitamin-A-related corneal destruction is disturbing in light of the proliferation of such programs.

This study was a retrospective review of hospitalized cases, and may not accurately reflect the incidence or characteristics of vitamin-A-related corneal destruction in the population at large. The findings are consistent, however, with those of the country-wide prevalence survey.[6] The latter estimated 43 new surviving cases in the country per year or, with the generally accepted mortality of 50%, 86 cases annually. One of the three patients seen in the field had been treated at Bloom Hospital, for an estimated 30 cases a year at that facility. In addition, there was close agreement on the age distribution and rural-urban differential of active cases.

Summary

A retrospective review of 3,490 admissions to the major pediatric facility in El Salvador was undertaken to determine whether biannual administration of massive doses of vitamin A (200,000 international units) to all available 1- to 4-year-old children was effective in preventing keratomalacia. During the 12 months preceding and following initiation of the program, the number of children admitted with presumed vitamin-A-related corneal destruction (33 vs. 31) and proportion of all malnourished admissions with such destruction (26 vs. 25 per 1,000) were similar. The seasonal distribution of these cases remained unchanged, the usual summer peak closely following the first distribution. Unexpectedly, 48% of the children had been ineligible for participation in the program, the vast majority being under 1 year of age. Only 80% of eligible children had actually received the vitamin.

Corneal destruction was invariably accompanied by severe, generalized malnutrition. Mortality among girls with corneal destruction (28 per 1,000) was almost three times that of boys, or malnourished patients as a whole.

Acknowledgments

We thank Humberto Escapini, M.D., our clinical consultant; Vilma deAparicio, M.D., and Luis Ochoa, M.D., for their advice and governmental coordination; and Julio Astacio, M.D., Minister of Health, government of El Salvador and Susan T. Pettiss, M.D., director of Blindness Prevention, American Foundation for Overseas Blind.

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TEMPORARY BLINDNESS AFTER COSMETIC BLEPHAROPLASTY

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Retrobulbar hemorrhage, a rare complication of cosmetic blepharoplasty to treat baggy eyelids, presumably leads to blindness by occlusion of the central retinal artery.[1-5] A patient had retrobulbar hemorrhage associated with a temporary complete loss of vision after the surgical treatment of dermatochalasis and orbital fat hernia.

CASE REPORT

A 60-year-old white man had three scleral buckle operations on his right eye to treat recurrent retinal detachments. After these surgical procedures, there was moderate dermatochalasis and herniation of orbital fat in all four eyelids and dermatochalasis over the cheeks (Fig. 1). The edema accompanying the scleral buckle operations apparently caused the skin to stretch and the orbital septum to separate from the aponeurosis of the levator palpebrae superioris muscle and the capsulopalpebral fascia.[6] Visual acuity was R.E.: 20/30, and L.E.: 20/25.

In June 1974, the patient underwent a cosmetic blepharoplasty to excise excessive skin and herniated orbital fat from all four eyelids. One percent lidocaine (Xylocaine) with epinephrine was injected subcutaneously into all four eyelids and an ellipse of skin was excised from both upper eyelids. Buttonholing the nasal orbicularis muscle and orbital fat capsule exposed the upper nasal orbital fat, which was then excised. In the lower eyelids an infralash skin incision extended from 2 mm temporal to the punctum to 1.5 cm beyond the lateral canthus. Dissecting skin from the orbicularis muscle to the level of the inferior orbital rim produced the skin flap. The orbicularis muscle was then incised just above the inferior orbital rim over the horizontal length of the eyelid, and prolapsed orbital fat was excised from all three fat pockets.

Orbital fat was excised from both upper and lower eyelids until it no longer prolapsed when gentle pressure was applied to each eye. Hemostasis was achieved by clamping the orbital fat with a hemostat, cutting the fat distal to it, and applying cautery with a Bovie apparatus to the hemostat. With a forceps, I grasped the orbital fat beneath the hemostat, as the hemostat was released, so residual bleeding from the fat was ruled out before it was released to retract into the orbit. The excessive skin of the lower eyelids was removed by excising a large triangle of skin laterally and a minimum 5-mm segment vertically.

More than usual bleeding occurred from the skin and orbicularis muscle of the right lower eyelid, while bleeding in the other three eyelids was average. Hemostasis of the skin and orbicularis muscle was achieved with the disposable Concept and Bovie cauteries and by pressure application of gauze pads soaked in 1% lidocaine with epinephrine. At the end of the procedure, there was no bleeding in all four eyelids. The skin was approximated with continuous 6-0 black silk sutures. A pressure dressing of gauze fluffs, an elastic bandage, and paper tape was applied to the eyelids, and the patient was returned to his room.

My routine at the time of this surgery was to leave a pressure dressing on the eyelids for 15 to 30 minutes postoperatively. Due to involvement in a subsequent case, two hours passed before the dressing was removed. The patient stated that he began to notice severe pain over his right eye as soon as he returned to his room, two hours previously. When the pressure dressing was removed, the right eye was severely proptotic, the eyelids were markedly extended, and the eye and eyelids were stony hard to palpation. Visual acuity was no light perception; there was no ocular motility. A right retrobulbar hemorrhage and secondary retinal artery occlusion was diagnosed, and the sutures were removed quickly from the right lower eyelid incision. Blood clots and fresh blood seeped from the right lower eyelid and orbit. The eye spontaneously became softer, the proptosis resolved, visual acuity returned to its preoperative level, and ocular motility improved.

The patient was returned to the operating room, and inspection of the right lower eyelid revealed minimal oozing of blood from at least 15 sites on the skin flap and orbicularis muscle. There was no active hemorrhage from the orbital fat, although



Fig. 1 (Putterman). Preoperative appearance of patient with dermatochalasis and orbital fat hernia of all four eyelids and dermatochalasis of cheeks secondary to edema from scleral buckle procedures.

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Fig. 2 (Putterman). Appearance of patient after cosmetic blepharoplasty complicated by retrobulbar hemorrhage and temporary blindness. Residual cheek skin may be treated by excision of an ellipse of cheek skin.

there were clots in the orbit; this was presumably from the orbicularis muscle and skin hemorrhage passing through the orbicularis incision site into the orbit. Hemostasis was achieved with the Bovie and Concept cauteries and the surgical area was observed. Approximately ten minutes later, hemorrhage spontaneously reappeared in nearly every area previously coagulated. Hemostasis was again achieved, and a drain was placed between the skin flap and orbicularis muscle exiting from the lateral canthus incision site. The skin was resutured with continuous 6-0 black silk. No dressing was applied, but the patient and nurses applied ice-cold compresses to the eyelids over the next 24 hours. Blood oozed from the right lower eyelid drain for another 12 hours and then subsided.

Results of a complete physical examination, hematologic analyses, and T_4 and T_3 serum uptake were normal. The postoperative result was satisfactory, and central and peripheral vision, ocular motility, and pupillary responses were similar to the preoperative status (Fig. 2). The patient had excessive skin over the cheeks, which may be excised by removing an ellipse of skin from each cheek at another time. However, he was satisfied with his appearance and declined further surgery. (Attempting to remove cheek skin using the routine cosmetic blepharoplasty procedure commonly leads to ectropion, and it is therefore usually better to correct excessive cheek skin with a secondary procedure.)

Discussion

Although a relatively rare occurrence, blindness has been reported after cosmetic blepharoplasty, and central retinal artery occlusion from a retrobulbar hemorrhage has been implicated as the cause.[1-5] Advocated treatment varies from immediate paracentesis of the anterior chamber to observation.

In the present case, neovascularization of the eyelid tissue secondary to the three scleral buckle operations may have led to the unusual persistent bleeding. Another explanation is that the epinephrine in the lidocaine, both injected and applied with pressure, may have led to temporary vasoconstriction of blood vessels; when the chemical effect dissipated, a rebound vasodilatation may have led to rebleeding. However, the use of lidocaine with epinephrine is routine and has not resulted in retrobulbar hemorrhages in more than 200 cosmetic blepharoplasties by the same technique.

Barker[7] observed the dissected planes in rhytidectomy (face lift) surgery for 30 minutes after hemostasis was achieved. In 62 cases, moderately severe bleeding recurred in sites previously controlled by cauterization and ligation. This was similar to the rebleeding that occurred in the coagulated blood vessels at reoperation in my patient.

To prevent a retrobulbar hemorrhage, all oozing vessels must be controlled with cautery. The use of plain lidocaine, rather than lidocaine with epinephrine, to prevent rebound vasodilatation, must certainly be considered, but the benefit of prolonged anesthesia and hemostasis from lidocaine with epinephrine is important in most patients and makes this a preferable anesthetic. Nevertheless, even with these precautions, bleeding can recur from cauterized blood vessels.[7]

Presumably, the pain noted by the patient when he first returned to his room after surgery was the increase in intraocular pressure secondary to the retrobulbar hemorrhage. If this was so, it is possible that the patient had no light perception due to a central retinal artery occlusion for two hours. The complete return of vision therefore suggests that blindness from a central artery occlusion can be reversed as long as two hours after its occurrence.

Since a retrobulbar hemorrhage and central retinal artery occlusion from rebleeding of cauterized blood vessels is a possible, uncontrollable complication of all cosmetic blepharoplasties, early detection of the retro-

bulbar hemorrhage is the best solution to prevent blindness. The pressure dressing in this patient masked the presence of the retrobulbar hemorrhage and prevented its early detection. Therefore, I no longer use a dressing after a cosmetic blepharoplasty. Instead, gauze pads soaked in iced saline are applied in the operating room and intermittently for 24 hours postoperatively. For the first two hours postoperatively, the nurse checks the patient every ten minutes for ocular pain, proptosis, and loss of vision. Should any of these signs and symptoms occur, the surgeon or resident is called immediately. If a retrobulbar hemorrhage with loss of vision occurs, I recommend opening the incision site and inspecting the wound since it successfully reversed the blindness in this patient.

Summary

A patient who underwent a cosmetic blepharoplasty suffered a retrobulbar hemorrhage with no light perception detected when the dressing was removed two hours postoperatively. Opening the incision site led to the complete return of visual acuity and ocular motility and relief of the proptosis.

The rebleeding of cauterized blood vessels may have caused the retrobulbar hemorrhage and seems to be a potential problem in all cosmetic blepharoplasties. Eliminating the use of postoperative bandages may prevent blindness after cosmetic blepharoplasty since it allows early detection of a retrobulbar hemorrhage. This allows the nurse to check the patient for loss of vision and proptosis at ten-minute intervals for the first two hours after surgery so immediate treatment can be implemented if retrobulbar hemorrhage and central retinal artery occlusion occur.

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NOTES, CASES, INSTRUMENTS

SIMPLIFIED NO PRESSURE EYELID RETRACTOR FOR CATARACT SURGERY

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The separate eyelid retractor* is simple, inexpensive, has no exposed metal parts that can be accidently pressed on to cause pressure on the globe, and has a solid blade that eliminates or prevents the protrusion of eyelashes into the operating field (Figure). It also has a small round protruding metal ball, around which the superior rectus muscle fixation suture may be hung with variable amounts of traction, with the weight of a serrefine clamp lying over the temporal area.

For many years, Castroviejo[1] has been using separate eyelid retractors for intraocular surgery. Recently, Jaffe[2] and Newell[3] described their preferred types of individual eyelid retractors. All of them are fixed to the eye drapes by mosquito clamps, the former two by sutures tied to the eyelid retractor, the latter by a rubber band attached to the eyelid retractor. All produce considerably less pressure on the globe in certain cases where pressure on the globe can be noted with a full type of single speculum, such as the Park, Guyton-Park speculum, and the Maumenee-Park speculum. The retractor is merely the solid blade of the Park speculum with a heavy long black silk suture tied to it.

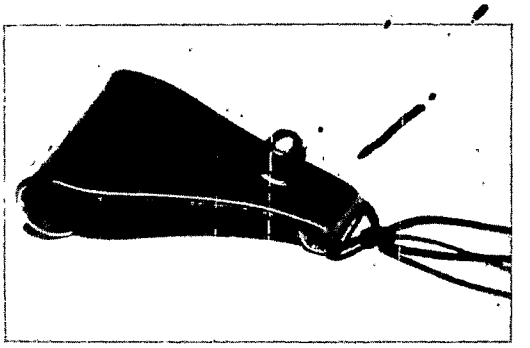


Figure (Osher). Simple solid-blade separate eyelid retractor.

This eyelid retractor does not have the protruding screw of the Castroviejo eyelid clamp that frequently gets in the way, sometimes everts the tarsus, and has to be positioned in four different areas for good and evenly distributed eyelid retraction. There is no contact whatsoever with the globe and one can put as much traction as desired on the eyelids by way of the mosquito or serrefine clamp-held suture.

SUMMARY

A simple, inexpensive, individual, solid blade eyelid retractor has no contact with the globe, produces no pressure on the globe, and eliminates the eyelashes from the operating field.

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* Instrument provided by the Storz Instrument Company, St. Louis, MO 36122.

MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

SEVENTEENTH ANNUAL RESEARCH MEETING OF THE DEPARTMENT OF OPHTHALMOLOGY OF THE UNIVERSITY OF TORONTO

The 17th Annual Research Meeting of the Department of Ophthalmology, University of Toronto, Toronto, Ontario was held on June 12, 1975, in the Medical Sciences Building of the University of Toronto. The meeting was inaugurated by H. Stancer, Head of Research, Clarke Institute of Psychiatry, Toronto, Ontario. The guest of honor was D. H. Hubel, Professor of Neurobiology, Harvard Medical School, Boston, Massachusetts. Abstracts of the papers presented are as follows:

OCULAR EFFECTS OF ORBITOCRANIOFACIAL SURGERY

G. M. Barban, L. A. Lloyd, and J. R. Buncic (Toronto)

Of 31 patients who had orbitocraniofacial reconstructions performed during the last four years at the Hospital for Sick Children, Toronto, all patients with proptosis improved, and visual acuity remained unchanged with one exception. Hypertelorism was improved to normal in all cases, although one patient required further correction. Fifty percent of the patients became more esotropic after surgery.

THE PREVENTION OF AUTOLYSIS OF STORED CORNEA USING CORTICOSTEROID AS A LYSOSOME MEMBRANE STABILIZER

T. J. Chin-Fook, N. S. Ranadive, and P. K. Basu (Toronto)

Many eyes donated for use in corneal grafting are rejected because of signs of autolysis in the donor material. The purpose of this experimental study was to determine whether hydrocortisone acting as a lysosome membrane stabilizer could prevent or retard autolysis of the corneas under storage, and if so, what was the most efficacious concentration.

Different groups of rabbit corneas were placed in saline as controls or in varying concentrations of hydrocortisone (10^{-10}M to 10^{-4}M at pH 7.4) at 37 and 4°C. Acid phosphatase released after six hours was measured biochemically. This enzyme was used, as a marker enzyme reflecting lysosomal labilization.

Results showed a significant stabilization of the lysosomal membrane at 4°C as compared to 37°C. A trend toward stabilization of the lysosomal membrane was seen when 10^{-8}M concentration of hydrocortisone at 37°C was used, there being no demonstrable stabilization at 4°C.

CORNEAL CHANGES IN PRIMARY CONGENITAL GLAUCOMA

W. R. Coughlin and J. D. Morin (Toronto)

A new technique was developed for measuring small changes in horizontal corneal diameter in cases of primary congenital glaucoma by utilizing a contact lens and color photography.

A controlled study of such cases suggests that following good control of intraocular pressure one may monitor changes in horizontal corneal diameter as an index of underlying disease progression. A decrease in horizontal corneal diameter was obtained at a time when the normal eye is continuing to grow and irrespective of the age of onset of the clinical presentation of the disease, suggesting that other factors may play a significant role in the clinical picture.

Scleral Collagen in Young and Adult Normal Human Eyes

W. R. Coughlin and J. D. Morin
(Toronto)

A pilot study of scleral collagen in young and adult normal human eyes revealed similarity in the proportion of immature, labile, and mature collagen but marked dissimilarity in the percentage of acid soluble (labile) scleral and nonscleral collagen (55-60% vs. 10%). Corroborative evidence of a high acid soluble collagen pool was obtained from an analysis of the types of cross linkage formation in the young and adult human sclera. A high acid soluble labile collagen pool may be significant in the pathogenesis of congenital glaucoma and myopia.

Fluorescein Angiographic Review of Diabetic Maculopathy

P. G. Flora and C. B. Mortimer
(Toronto)

A review of fluorescein studies done on diabetics with background retinopathy and no disk involvement disclosed a classification of (1) normal macula; (2) edema; (3) microaneurysms; and (4) macular exudates and corresponded to progressively decreasing vision. When color fundus photographs were compared to fluorescein studies a good correlation was evident in over 50% of cases. In a follow-up study, despite treatment, visual acuity decreased in over 50% of cases and this was correlated to fluorescein changes.

An Evaluation of the Pattern Visual Evoked Response

S. Herzig and J. A. Parker (Toronto)

The pattern visual evoked response was evaluated as an objective test of visual loss due to macular disease. The effects of refractive error vs. macular disease on the pattern visual evoked response were compared. Refractive error was found to affect primarily the latency of the response with a decrease in amplitude occurring only with visual acuities of 20/300 or less, while a completely flat response was obtained with macular disease at visual acuities as good as 20/40.

The pattern visual evoked response may prove to be an excellent objective test of binocularity, as the response with both eyes open has a shorter latency and greater amplitude then either eye tested alone. The pattern visual evoked response has characteristics dependent on the individual tested, which results in a wide range of normal. Part of this individuality is due to the variable amounts of alpha rhythm picked up at the occiput during the recording of the pattern visual evoked response. Future work will be aimed at elimination of the electrical "noise."

Contrast Grating Acuity for Detection of Macular Disease in the Presence of a Cloudy Media

S. Herzig and J. A. Parker (Toronto)

A clinical test for detecting the presence of macular disease in patients with cloudy media and only moderate loss of visual acuity, that is, 20/25 to 20/80 consists of presenting the patient with a grating in which the contrast between dark and light bars can be varied. The ratio of the percent contrast at which the patient sees the smallest bars (16 c/d) to the percent contrast at which the 4 c/d bars are seen was examined. In patients with pure macular disease, this ratio ranges from 2.5:1 to 11.2:1. In patients with cataract only, this ratio is less than 2.5:1. In those with both macular disease and cataract, the ratio is greater than 2.5:1 but does not extend into the high ranges of pure macular disease unless the macular disease is the dominant cause for the loss of visual acuity.

Predictability of Risk of Chronic Iridocyclitis in Juvenile Rheumatoid Arthritis. A Retrospective Study

N. L. Lipton, J. S. Crawford, M. L. Greenberg, J. E. Boone, and H. B. Stein (Toronto)

Juvenile rheumatoid arthritis may be complicated by chronic insidious iridocyclitis. Unless diagnosed and treated early, such sequelae as band keratopathy, cataracts, and secondary glaucoma may ensue. Patients with juvenile rheumatoid arthritis who develop chronic iridocyclitis tend to be those with pauciarticular disease (involvement of five or fewer joints) and a positive antinuclear antibody (ANA) test. To assess how well these criteria would enable predictability of risk of chronic iridocyclitis in patients with juvenile rheumatoid arthritis, a retrospective study of 14 patients with juvenile rheumatoid arthritis complicated by chronic iridocyclitis (Group 1) was conducted, utilizing an equal number of juvenile rheumatoid arthritis patients without chronic iridocyclitis as controls (Group 2). The incidence of pauciarticular disease was 79% in Group 1 compared to 36% in Group 2 and 93% of Group 1 were ANA-positive compared to 14% of Group 2. On the basis of this study, the patient with juvenile rheumatoid arthritis most likely at risk for chronic iridocyclitis has pauciarticular disease and a positive ANA test. This is the patient with juvenile rheumatoid arthritis who should be seen frequently by the ophthalmologist so that if chronic iridocyclitis develops, it may be diagnosed and treated early.

Effect of Near Ultraviolet Light on the Synthesis of Protein in Rat Retinas

P. Lou, Y. Matuk, and J. A. Parker (Toronto)

The effect of near ultraviolet light on the incorporation of tritiated leucine into the proteins of a cell-free system obtained from the retina of albino rats was studied.

Irradiation with a Black Light fluorescent lamp, which has a light intensity of 140 $\mu W/cm^2$ and emits maximally at 350 nm, caused more than 90% inhibition of protein synthesis. Irradiation using monochromatic light at an intensity of 220 $\mu W/cm^2$ showed 80% inhibition of protein synthesis at a wavelength of 320 nm, 53% inhibition at 340 nm, and 15% inhibition at 360 nm. Retinol enhances the effect of ultraviolet light.

Dacryocystometry

H. J. Smirmaul and J. C. Hill (Toronto)

The objective of this study was to determine the dynamic pressure variations which occur during blinking within the excretory part of the lacrimal system that may be used to identify and locate dysfunctions of the lacrimal pump.

In 50 patients, the lower canaliculus was intubated using a soft Silastic tube connected to a strain gauge transducer with strip recorder output. The tracings obtained were analyzed and rearranged in a matrix to facilitate diagnosis and location of the relevent pathology. The patterns obtained at different locations along the lacrimal system can be explained in terms of the balance of action of the two components of the lacrimal pump. Obstructions, either stenosis or complete blockage, can be accurately located along the path of tear transport.

It was found that dacryocystometry can be a useful, atraumatic diagnostic test in the evaluation of the excretory part of the lacrimal system, especially before planning corrective surgical procedures.

Ocular Complications in Children With Postrenal Transplants

G. B. Walman, L. D. J. Chisholm, and G. Arbus (Toronto)

A study of children with postrenal transplants was performed to compare the inci-

dence in posttransplant adults as well as children in other transplant programs. The main objective was to determine the relationship of systematic corticosteroid dosage to the onset of cataracts.

Forty-one cases of patients ranging from age 3 to 20 years at time of transplant were evaluated. Sixteen children had posterior subcapsular cataracts (bilateral). Numerous variables were analyzed for possible effects on onset of cataracts. Total cumulative dose was found to be the most important factor in cataract formation.

The corticosteroid dosage in our children was considerably lower than most other pediatric programs and our lower incidence of cataracts probably reflects this factor. We feel it essential, therefore, that nephrologists reevaluate the need for high corticosteroid dosages in prevention of renal allografts.

Immunological Mechanisms in Corneal Graft

A. L. MacDonald and P. K. Basu (Toronto)

The objective of this study was to demonstrate the presence of "killer cells" in the host during corneal allograft reaction in rabbits. For this purpose an in vivo and an in vitro assay were used.

Unilateral keratoplasties with eccentrically placed full thickness grafts, 7.5 mm in diameter, were performed using outbred rabbits as donors and recipients. Lymphocytes obtained from the host's spleen, preauricular lymph nodes, and peripheral blood were purified. The cells were then tested for killer cell activity with the two assays.

The in vivo assay consisted of injecting an equal number of lymphocytes into the anterior chamber of the remaining eye of the original donor as well as into the anterior chamber of the original host (control), and that of a normal unrelated rabbit (control). At desired intervals after the operation, rabbits showing graft reaction were sacrificed and the corneas removed and assayed for endothelial cell damage by using a quantitative dye (trypan blue) exclusion test. The damage to the donor specific endothelium was significantly greater than the damage to the endothelia of the host and unrelated animals ($P < .001$).

For the in vitro assay, target cells were prepared by establishing tissue cultures from the original donor cornea. The donor corneal cells were labeled with radioactive chromium 51 and incubated with either lymphocytes from the corresponding host at the time of corneal graft reaction, or from an ungrafted animal. After incubation, the radioactivity of the supernatant was measured with a gamma-counter.

There was a significant release of chromium from the donor cells when they were challenged with the host specific lymphocytes (specific cytotoxicity $> 25\%$).

A Scotopic Perimeter for the Evaluation of Night-Blindness

J. A. Parker, J. Arndt, P. Hallet, and E. Orpin (Toronto)

A Rayner arc perimeter has been modified to perform kinetic fields one log unit above rod threshold. A filtered argon lamp provides ultraviolet to irradiate a fluorescent test object. The patient fixates on a far red L.E.D. lamp, and the technician monitors fixation with a portable infrared night scope. Normal scotopic fields to a 1-degree object are almost as full as the photopic fields. Rod dystrophies show profound constriction of field in the dark. Early rod dystrophies, normal by dark adaptation, electroretinography, and ophthalmoscopy show cuts in the scotopic fields.

A Pigmented Membrane in the Anterior Chamber After Surgery

J. S. Speakman and M. Ghosh (Toronto)

A pigmented membrane developed on the posterior surface of a cornea after treatment of a penetrating injury. The eye was enu-

cleated and the posterior surface of the cornea at the site of the membrane formation was examined by electron microscopy. The pigmented membrane consisted for the most part of a single layer of corneal endothelial cells packed with pigment granules. The granules were large and round indicating their origin from the neuroectodermal epithelium of the iris. In one small area a clump of loosely arranged pigmented cells was found with multiple villous processes that could represent an extension of pigment epithelium over the posterior surface of the cornea. In constrast to previous reports the pigmented membrane in this case consisted almost entirely of corneal endothelial cells containing pigment derived from neuroectodermal epithelium.

Surgical Treatment of Brown's Syndrome

J. S. Crawford (Toronto)

In 1950, Dr. H. W. Brown reported the superior oblique tendon sheath syndrome and the cutting of the sheath as treatment for the condition. My results with similar surgery have been disappointing. Consequently different operations have been carried out on true Brown's syndrome to lengthen the tendon. These consisted of Z tenotomy, split tendon lengthening, and complete tenotomy of the superior oblique tendon.

On the basis of this investigation it would seem that the superior oblique tendon and not the sheath is the major factor. Tenotomy of the superior oblique tendon seems to offer a safe and effective surgical treatment for true Brown's syndrome.

Changes of Ocular Dominance Columns in Monocularly Deprived Monkeys

D. H. Hubel, T. N. Wiesel, and S. Levay (Boston)

We investigated the effects of enucleation of one eye and of monocular closure in newborn monkeys. The animals were examined at about 1½ years of age. In two enucleated animals microelectrode penetrations along layer IV C of the striate cortex gave continuous unit activity that was influenced from the remaining eye; there were no obvious silent regions corresponding to the columns of the removed eye. The morphology of the ocular dominance columns was investigated by making lesions restricted to a single layer of the lateral geniculate body and then staining the striate cortex for degenerated terminals after four- to five-days' survival time. After a lesion in a layer receiving input from the remaining eye there was widespread degeneration and only occasional small gaps with no degenerating terminals. A similar lesion in a deafferented layer of the lateral geniculate body produced a complementary pattern with only small patches of sparse degeneration. A change in the ocular dominance columns was seen also in a monkey raised with one eye occluded. The physiology showed that in superficial and deep layers the majority of cells responded only to stimulation of the normal eye. In layer IV C cells did respond to the deprived eye but over abnormally small regions; the areas with cells responding only to the nondeprived eye were by contrast much larger than normal. The ocular dominance columns were also examined by two anatomical methods. One took advantage of the phenomenon of transynaptic transport, visualizing the ocular dominance columns autoradiographically. In the second method tangential sections through layer IV C were stained according to Liesegang's reduced silver method. Both methods showed a marked reduction in the width of the deprived columns and a corresponding increase of the columns with input from the normal eye. Thus monocular deprivation early in life led to a drastic rearrangement of the ocular dominance columns, presumably through branching or sprouting of the normally activated geniculate terminals at the expense of the deprived terminals.

Functional Architecture of Primary Visual Cortex in the Normal Monkey

D. H. Hubel and T. N. Wiesel (Boston)

Single cells in the monkey striate cortex may be characterized in a number of different ways, including complexity, receptive field size, and position in the visual field, receptive-field orientation, and ocular dominance. A study of the architecture begins by asking whether cells are scattered through the cortex at random with respect to these variables or arranged in any systematic way. The results show a remarkable degree of order and intricate patterning. Cells of like complexity tend to be segregated to some extent by layers. Cells with fields in a given part of the visual field are grouped according to the well-known topographic map. Field size and magnification are closely related to distance from the fovea, so that the visual field displacement corresponding to a 1-mm movement along the cortex increases in a way closely paralleling the increase in field size. Cells of like orientation and cells of similar ocular dominance are grouped in two independent systems of slab-like structures ("columns"). Orientation slabs are about one-tenth the width of ocular dominance columns, but the size of a complete set of columns (left plus right, or a full 180 degrees) is similar in the two systems being 0.5 to 1 mm and showing no obvious variation in different parts of the cortex. Thus, a 1- to 2-mm displacement anywhere along the cortical surface is sufficient to displace the receptive fields into an entirely new region and also to analyze the retinal image in all orientations and with both eyes.

In layer IV C cells are almost exclusively monocular, and the majority have small center-surround concentric receptive fields. On crossing an ocular dominance column in IV C the fields progress in an orderly manner through the visual field, but at the border there is a discontinuity; the field position in the new eye shifts back to about the midpoint of the path just traversed in the other eye; this ground is covered once more and then an additional equivalent distance is traversed. The eyes then shift; the old eye takes up where it left off. The visual fields in the two eyes are thus interlaced and in each column the magnification is anisotropic, with a value (in millimeter per degree) that in a direction transverse to the column is double that in the direction parallel, that is, double the overall value.

P. K. Basu

THIRD CHARLOTTENLUND OPHTHALMOLOGICAL CONFERENCE

Twenty-eight ophthalmologists from Europe and the United States met by invitation in the Third Charlottenlund Conference, Sept. 2-6, 1975. The meetings began in the elegant Hotel d'Angleterre in Copenhagen in a series of conferences arranged by the organizing committee: Jørn Boberg-Ans of Denmark; Jürg Draeger of West Germany; Dermont Pierse and Michael J. Roper-Hall both from England.

The conference opened with a discussion of technical advances in glaucoma microsurgery followed by a discussion of techniques in corneal incision in cataract surgery. J. Kersley gave a report on the use of a new soft lens which is 85% water and has a high oxygen permeability. This lens is fitted to cataract patients immediately at the end of surgery, and patients are returned to their rooms without an eye patch. In 100 patients who received the lenses, six lenses were removed early because of surgical problems. One patient suffered an infection that was probably not because of the lens, and a few patients rubbed out the lens and lost it in the first 24 hours after surgery (while still groggy from preoperative medications). Fifty of the patients had the lens removed and refitted six weeks postoperatively for refractive changes. Only one patient had given up the use of the lens. The lenses had been

in continuous use in these patients for periods ranging up to ten months and seemed to be providing a satisfactory solution to the problem of the correction of monocular aphakia. Because of their fragility, the lenses themselves were difficult to handle and could not be removed or inserted by the patient.

C. D. Binkhorst reported on the rate of retinal accidents in pseudophakic patients followed for three to four years. He found that extracapsular cataract extraction gave strikingly better protection for the retina than intracapsular cataract extraction both from the standpoint of a lower incidence of retinal detachment and a lower incidence of cystoid maculopathy.

Yale Fisher led an interesting discussion on the use of ultrasound in ophthalmology and pointed out that drusen of the optic nerve yielded a peculiarly intense echo pattern, presumably because they are calcified. Ultrasound is uniquely capable in the differential diagnosis of these lesions.

On Thursday afternoon the conferees were treated to a delightful excursion with stops to visit Viking ship ruins and the like, as they moved to their second meeting place at the Hotel Hesselet on the Island of Funan. There was an almost unbelievable attention to details by the wives of the Danish ophthalmologists who made every day a delightful experience for the delegates and their wives.

The conference continued on Friday with beautiful examples of photographs of the corneal endothelium in donor corneas by Witmer, and in patients by T. Zimmerman (representing Kaufmann's group). There was a long and spirited discussion concerning lens implantation during the rest of that day's conference.

The conference opened on Saturday with a detailed discussion of the problems of astigmatism following cataract surgery, led particularly by Boberg-Ans, Epstein, and Charleux. Charleux reported on his preliminary trials at intracorneal suturing. Although theoretically most interesting, most of the conferees agreed that this would take someone of Charleux's skill to perform with the necessary accuracy. A detailed discussion followed on many phases of cataract surgery and corneal grafting. Witmer discussed the antigenic properties of the various layers of the cornea, and the preservation of graft material, particularly endothelium, using HEPES buffer for tissue culture storage media.

On Friday afternoon the group had a bus tour of the island of Funan and a 4-o'clock "luncheon" at the home of Mr. Jungard on the island of Faenø. This was an idyllic spot: a farm, and hunting and game preserve. Mr. Jungard and his family were most enthusiastic hosts and our visit to their island provided a fitting social climax to the week.

The participants carried back with them not only an increase in knowledge and the stimulation such a close confrontation can provide, but also a tired but happy appreciation of the beauties of Denmark and the graciousness of those who made this meeting possible, particularly our immediate hosts, Dr. and Mrs. Boberg-Ans.

ROBERT C. DREWS

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Published monthly by the Ophthalmic Publishing Company
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HERPETIC STROMAL DISEASE

Although the pathogenesis of epithelial herpes seems limited to cell death caused by direct invasion of multiplying virus, the questions of the causes of the clinical stromal disease and iritis, and the causes of susceptibility to recurrences, remain unclear. Most workers agree that the whitish opaque necrotizing stromal disease seen under dendritic ulcers, or in larger more chronic herpes infections, almost always harbors live virus within the keratocytes, although immune factors may be partially responsible for some of the tissue destruction seen. Certainly there is no questioning the fact that virus can invade keratocytes and reside within the stroma. All available evidence indicates that in corneas which undergo acute melting from herpes this is a major factor, and in the white necrotizing stromal disease direct virus invasion is generally encountered. On the other hand, stromal cells can be rapidly repopulated and the death of keratocytes alone probably cannot account for the stromal necrosis and sequestration of collagen seen in this disease or the inflammatory cell attracted to the lesion. Although viral in vasion must play a primary role, immun factors cannot be discounted. When ce death occurs in the absence of immune fac tors, we would expect a clinical picture suc as that seen in patients who receive lamella keratoplasties with dead (frozen or glyceri preserved) corneal tissue, or a picture simila to that seen after cell death caused by cryo genic treatment of the cornea. This is cer tainly not the clinical picture of herpes, an immune factors must be involved.

The importance of immune factors i probably greatest in the disciform edema o herpes and perhaps in the iritis. Some tim ago, such factors were not considered a being primary factors in the pathogenesi of disease. Because of this, our group showe that typical delayed hypersensitivity coul occur to herpes antigens; that the injectio of the antigen into sensitized recipient ani mals could cause a transient corneal edema and that the superficial infection of sensitize animals could cause a disciform edema-lik

picture when the same kind of infection in nonsensitized animals had no such stromal effect. This work did not imply that delayed hypersensitivity was the only possible cause of such disciform edema, nor did it imply that other immune factors could not be involved. It did call attention to the immunopathology of this phase of herpes and the importance of factors such as delayed hypersensitivity in its etiology.

Since that time, patients with disciform edema and iritis have been shown to have viral antigen in the white blood cells of their anterior chamber. They have also been shown by us to have cell-free virus in the anterior chamber fluid, and yet we have not been able to culture living virus from the anterior chamber fluid. There have been few reports of positive cultures of living virus from the anterior chamber fluid, in spite of the fact that we know virus is there, and many attempts at culture have been made. One explanation is the possibility that virus antibody complexes in the anterior chamber may be toxic to the endothelium. In dogs such virus antibody complexes clearly cause a disciform edema-like picture commonly seen in canine infectious hepatitis. Animals with canine infectious hepatitis even have an iritis and a disciform edema that is corticosteroid responsive in the same way that human disciform edema is responsive to small doses of corticosteroid. Although either delayed hypersensitivity or virus antibody complexes may cause such a syndrome, possibly multiple factors are involved that will require further study to clarify. It is of clinical importance, however, that the disease of disciform edema is different in its manifestations and drug responsiveness from necrotizing keratitis and that the factors involved, whatever their precise nature, are sensitive to corticosteroids and capable of suppression. There is one experimental drug, intravenous adenine arabinoside, which is at least partially effective in treating deep stromal disease and iritis. It may be that the pathogenesis of disciform edema and iritis will not become clear until even more potent antivirals are available and we can be pharmacologically certain that virus multiplication has been completely suppressed.

A final puzzling part of the problem of herpes involves recurrences of herpes simplex. At one time circulating antibody levels were thought to be of prime importance in determining which people would have recurrences and which would not. It was found, however, that recurrence rates and the onset of disease seemed independent of circulating antibody levels and that most people with recurrences had high stable titers of neutralizing antibodies. Our group found that there was locally produced gamma A antibody to herpes. This is a potent antibody, produced by plasma cells under the conjunctiva and secreted by the conjunctival epithelial cells. It could easily be stimulated to high levels by the instillation of innocuous dead herpes virus. There was hope that the stimulation of such local antibody production might be more important than circulating antibody and might prevent recurrences. Unfortunately, experimental studies have not borne this out. The popular new theory is that cell mediated immunity may determine who gets herpes and who does not. Present evidence indicates that in the absence of necrotizing corneal scars, recovery from herpes is not associated with persistence of virus in the stroma. Virus has been found in the trigeminal ganglion of both rabbits and man, and it appears from the work of Stevens, Nesburn, and others that this ganglion represents a reservoir for herpes virus. This is not in itself sufficient, however, to explain recurrences of herpetic disease. We have shown that both animals and humans secrete herpes intermittently in both tears and saliva. Although the trigeminal ganglion may be the reservoir, at least in part, for such virus secretion, many secretors never develop clinical disease. Why then do some suffer from recurrences of herpes, and others who secrete just as much virus in their tears and saliva do not. Many ex-

planations are possible, but one of the most popular is that cell mediated immunity to virus disease may differ in the two groups. Some studies suggest that a decrease in the ability of the key lymphocytes to rid the body of virus, may make us more susceptible to virus infection and that recurrent herpes represents a defect in cell mediated immunity. Other studies, equally inconclusive at the moment, suggest that delayed hypersensitivity (the other side of the cell mediated immunity sword) may be increased in those who get recurrent herpes, making immune damage a factor in the production of recurrences in secretors who become symptomatic. At present, this subject is difficult to resolve because our measurements of cell mediated immunity are indirect, often conflicting and not necessarily related to cellular antiviral activity. When such measurements as blast transformation (the stimulation of lymphocytes by virus) or the production of macrophage migration inhibitory factor (presumably related to the lymphocytes' ability to stop the migration of macrophages and congregate them at a lesion) disagree with each other and disagree with other measurements of key lymphocyte activity to viral antigen, how do we interpret these? Which are really relevant, if any, to the cells' ability to rid us of virus? An assay of cellular activity has been recently developed which shows that in tissue culture (plaque assay), immune cells can prevent infection from spreading (reduce the size of plaques). It is presently unknown whether this attractive and more direct measurement will provide more comprehensible measurements of cell mediated immunity, just as it is unknown with certainty whether cell mediated immunity and changes in the level of its activity are really responsible for recurrences of herpes and the severity of the clinical disease. Fortunately, it may be possible to measure these factors now, and if, for example, cell mediated immune deficiencies can be shown to be involved in the disease, treatment by transfer factor (a soluble factor easily obtained from lymphocytes of immune individuals) is a therapeutic possibility. We must resist the tendency, however, to assume that this particular factor must be the crucial factor simply because we don't know what else to blame. This has been done in the past with other immune factors and has not been rewarding.

HERBERT E. KAUFMAN

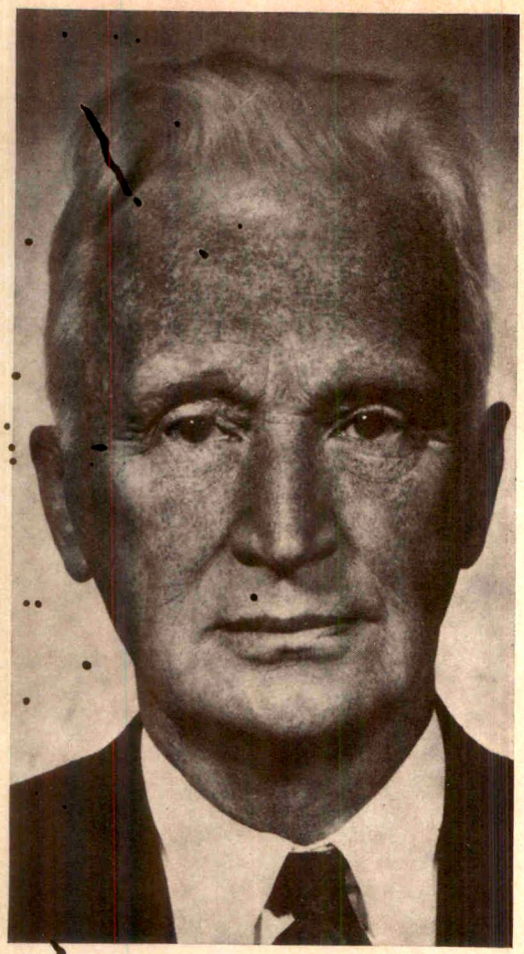
OBITUARY

LUDWIG J. K. VON SALLMANN, M.D. 1892-1975

Ludwig J. K. von Sallmann, one of the foremost research ophthalmologists of this century, died Sept. 24, 1975, in Washington, D.C., at the age of 83. He was a major contributor on experimental cataract and glaucoma and trained many of America's current generation of research ophthalmologists.

Born in Vienna, Dr. von Sallmann graduated from the University of Vienna Medical School. He took his ophthalmic training at the same institution and had the good fortune to be associated with such luminaries as Fuchs, Meller, and Lindner during his early professional years. In the early 1930s he served as assistant professor of ophthalmology at Peking Union Medical College in China; and before coming to this country in 1939, he became head of the Ophthalmology Department of the Empress Elizabeth Hospital in Vienna.

A vigorous opponent of Nazism, Dr. von Sallmann left his homeland at the outbreak of World War II. He was welcomed to this country by Dr. Hermann Knapp of New York City, founder of the Knapp Eye Hospital. Dr. von Sallmann served as director of the research laboratories of the Knapp Eye Hospital before joining the staff of the College of Physicians and Surgeons of



Ludwig J. K. von Sallmann, M.D.

Columbia University, where he later became professor of ophthalmology.

In 1955 Dr. von Sallmann became director of the Ophthalmology Branch of the National Institute of Neurological Diseases and Blindness in Bethesda. In the following 15 years he was highly productive in the fields of experimental cataract, glaucoma, and ocular immunology. He was a prolific writer, having authored more than 200 papers in his career. In the latest volume of "System of Ophthalmology," Sir Stewart Duke-Elder wrote:

> Much work has been done on the subject of experimental cataract for more than a century. On this subject Ludwig von Sallmann has not been surpassed by anyone in this generation.

Those of us who were fortunate enough to have been trained by Dr. von Sallmann at the National Institutes of Health owe an enormous debt to him. Highly knowledgeable in the basic sciences and greatly skilled in the arts of physical examination, ocular surgery, experiment planning, and data analysis, he strove to communicate his special talents to others. In all scientific matters he was highly critical, precise, and objective. His like will not be found with any great frequency among today's group of senior ophthalmologists, and his death represents a great loss to the profession. We mourn the loss of a great teacher, colleague, and friend.

G. RICHARD O'CONNOR

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper; with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

GONIODYSGENESIS

Editor:

With great expectations I read the article "Gonioscopic differences between primary open-angle glaucoma and normal subjects over 40 years of age," by R. Kimura and R. Z. Levene (Am. J. Ophthalmol. 80:56, 1975). The authors discuss important gonioscopic observations but seem to have missed some relevant observations in previous reports. Angle malformation in glaucoma has been my particular interest and I coined the term goniodysgenesis as a key word in "Dominant goniodysgenesis with late congenital glaucoma" (Am. J. Ophthalmol. 74: 28, 1972). This term is more than a word, it is an entirely new concept with far-reaching consequences for the classification of open-angle glaucomas.

Goniodysgenesis is a specific genetic

trait inherited in an autosomal dominant mode; it shows varying expressivity. The role of goniodysgenesis in open-angle glaucoma is frequently underestimated; it is therefore most refreshing to find this subject brought up again.

However, the subject is better documented than suggested by the choices of references in the article by Drs. Kimura and Levene.

TORD JERNDAL, M.D.
Göteborg, Sweden

REPLY

Editor:

Both our studies and those of Dr. Jerndal are similar in that they concern congenital malformation of the angle in open-angle glaucoma. They differ in that Dr. Jerndal deals with glaucoma in patients under 40 years of age (juvenile and late congenital), whereas we deal with glaucoma in patients over 40 (primary open-angle). His population consists of members of one family, whereas ours consists of individuals from different families. His angle malformation (goniodysgenesis) seems to be different in many respects from that noted by us. Dr. Jerndal's excellent study should have been included in our paper and we regret this oversight.

RALPH Z. LEVENE, M.D.
Birmingham, Alabama

JUVENILE RHEUMATOID ARTHRITIS

Editor:

I read the paper "Ocular manifestations of juvenile rheumatoid arthritis," by L. T. Chylack, Jr., D. C. Bienfang, A. R. Bellows, and J. S. Stillman (Am. J. Ophthalmol. 79:1026, 1975), with both interest and disappointment. The interest was aroused by the large series of 36 children followed-up for a mean period of 6.3 years; in this condition too few patients are often followed-up for too short a time.

The disappointment followed however on finding that the authors had failed to make the essential distinction between acute and chronic iridocyclitis.[1] Since the acute inflammation, adequately treated, had a good visual prognosis, and the chronic inflammation, however intensively treated, has a bad one[2,3] this failure affects the value of many of their findings.

Since 1968, I have been treating children much in the way described in this article, and now have a series of 61 patients with chronic anterior uveitis, followed-up for a mean period of 11 years. My results are so much worse than the claim in this paper of "no serious visual acuity loss and other complications in better than 80%" that, while congratulating the authors, I search for an explanation. Is it that a high proportion of their patients had acute iridocyclitis, or perhaps the benign type of chronic inflammation which I described in 1972?[2] Or is it possible that six years is too short a period in which to make pronouncements about prognosis?

Their statement that laboratory studies are not helpful in detecting iridocyclitis is contradicted by a paper read at the American Rheumatism Association Meeting in 1972,[4] which established the importance of finding antinuclear antibodies in seronegative children as a guide to the identification of those likely to develop this serious eye condition.

The authors' statement that the result of surgical treatment of band keratopathy is discouraging is also incorrect. The removal of a corneal band by chelation is easy, safe, and satisfactory.[5]

It is discouraging that chloroquine and hydroxychloroquine can still be given to any patient for over six years continuously—with the almost predictable result of pigmentary changes in the central retina and permanent damage to sight. Iatrogenic disease of this type is readily preventable.[6]

W. K. SMILEY, M.D.
Tapelow, Maidenhead, Berks, England

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Editor:

In their article, "Ocular manifestations of juvenile rheumatoid arthritis," Chylack and associates noted that 41% of children with uveitis related to juvenile rheumatoid arthritis, "did not respond to more than six months of intensive topical treatment with corticosteroid drops." That is an extremely important observation and admission. Many ophthalmologists are determined to use ophthalmic topical corticosteroid preparations for all cases of uveitis regardless of whether or not they improve the inflammation.

The prognosis of cataract surgery in children with juvenile rheumatoid arthritis is poor. Any medication that promotes the formation of lens opacification and does not materially improve an intraocular inflammation should not be used. Many children with juvenile rheumatoid arthritis and smoldering chronic iridocylitis require only prolonged use of cycloplegics.

There are three forms of juvenile rheumatoid arthritis:

1. The acute systemic type is characterized by an acute onset of rash, fever, leukocytosis, and hepatosplenomegaly. It occurs especially between ages 1 and 3 years and predominantly affects boys. Initially there may be no arthritis. Iridocyclitis is uncommon.

2. The poly-arthritis type is usually acute in onset and is seen more frequently in girls. Classically, over five joints are inflammed. Uveitis may occur.

3. The pauciarticular or monoarticular type is insidious in nature. From one to four joints may be involved. Characteristically, the arthritis is minor. Uveitis occurs in as high as 30% of children in this group.

Schaller and associates[2] noted antinuclear antibodies in 52 of 69 children with rheumatoid disease and iridocyclitis. Certainly all children with juvenile rheumatoid arthritis should have periodic eye examinations by an ophthalomologist; however, being aware of the presence or absence of antinuclear antibodies and also of the type of juvenile rheumatoid arthritis (monoarticular), will alert the physician to those cases that require especially careful observation.

J. T. Coyle, M.D.
Bellevue, Washington

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Reply

Editor:

While Mr. Smiley's experience in this field is well recognized, we feel that our series of patients offers some new and significant perspectives on the problems of iridocyclitis in juvenile rheumatoid arthritis.

Mr. Smiley has emphasized the significance of differentiating between the acute and chronic forms of iridocyclitis.[1-3] As he states in his letter, the acute form "adequately treated, has a good visual prognosis, and the chronic inflammation, however intensively treated, has a bad one." While we grant that this classification may be an interesting retrospective maneuver when reviewing a large series of cases, we have not found it particularly useful in dealing with new patients and their parents. Some of the reasons for this are mentioned by Mr. Smiley himself: 9/15 of his cases of acute iridocyclitis had recurrences[1] and there were exacerbations in his series of chronic cases "so severe as to produce hypopon." Therefore, in dealing

with a new patient with juvenile rheumatoid arthritis, it is impossible to assign him assuredly to the acute or chronic group. In our series, the patients with the acute fulminant onset frequently required the longest and most intensive treatment. This is in marked contrast to Mr. Smiley's experience. One reason why his patients with acute cases may have responded so well to treatment is that he included a large number of patients with ankylosing spondilytis with iridocyclitis in his group of juvenile rheumatoid arthritis patients.[2] The iritis of ankylosing spondilytis has an acute onset and a satisfactory response to treatment. We believe it incorrect to include these patients within a series of juvenile rheumatoid arthritis patients. We have excluded all cases of ankylosing spondilytis from our series and feel there is good clinical and immunologic evidence for distinguishing between these two populations. One of us (J.S.S.) has documented the presence of a W27 histocompatability antigen in over 90% of patients with ankylosing spondilytis. The antigen was absent in a large series of patients with juvenile rheumatoid arthritis. Therefore, if ankylosing spondilytics are eliminated from Mr. Smiley's population of acute cases, he is left with a large number of recurrent cases, which he might as well call chronic.

Regarding the value of antinuclear antibodies in defining a population at high risk of developing chronic iridocyclitis, Mr. Smiley states that because "51/58 of (his) patients with chronic iridocyclitis had positive tests for antinuclear antibodies" it is a "useful prognostic test."[3] However, he is mistakenly applying conclusions gained from the examination of a subgroup to the population as a whole. When our paper was submitted, we did not yet have completed data on the value of the antinuclear antibody test. Since then, however, the group at the Robert Breck Brigham Hospital has obtained what we believe is a more useful application of this test. In a recent symposium, Stillman and associates[4] reported that 41% of patients with the oligoarticular form of juvenile rheumatoid arthritis had positive antinuclear antibody factors as opposed to 15% in the combined groups of systematic-onset and polyarticular juvenile rheumatoid arthritis. Comparing patients with and without uveitis, 52% of those with uveitis had a positive ANF as opposed to 35% of those without uveitis. This is not a particularly striking difference in incidence rates. However when quantitative titers were measured, 31% of patients with uveitis had an ANF titer of 1:160 or more as compared to 9% of patients without uveitis. Through the use of quantitative titers, it is possible to define the risk of a certain subgroup of juvenile rheumatoid arthritis patients developing uveitis. The risk of uveitis for a girl with oligoarticular arthritis, an ANF test with a titer of 1:20 or greater, and the onset of JRA between 1 and 2 years of age was 95.7.[4] In contrast, girls in the sudden and polyarticular groups with similar characteristics had risks of 77.9 and 84.7, respectively.[4] By combining factors of sex, age, and type of onset of arthritis, and the ANF titer, reliable prognostication can be done and groups at greatest risk can be defined.

Our statement that surgical treatment of band keratopathy "achieved" discouraging results was clearly referring to a case treated in 1940 with "scraping of the cornea." We are aware of the successes in treating this condition with chelating agents, however none of our patients had sufficiently severe keratopathy to need such therapy.

Mr. Smiley's comments about chloroquine and hydroxychloroquine correctly emphasize the caution needed in applying these drugs to a pediatric population. However, he failed to place in proper perspective the benefits and relative risks of such treatment. The incidence of retinal toxicity in less than 1% and is not great enough (in a population regularly scrutinized by ophthalmologists) to outweigh the therapeutic benefit and a chance for remission.[5] In our population no child developed retinal toxicity who entered the study

free of it. Our one patient entered the study with an extent early macular degeneration after having previously taken chloroquine for more than a year.

While we cannot offer an explanation for the low incidence of serious complications in our group of patients, the low incidence cannot be dismissed easily by claiming that it is an artifact of a brief follow-up period. Since compiling the data, another two years have passed without any change in incidence of serious complications.

LEO T. CHYLACK, JR., M.D.
DON C. BIENFANG, M.D.
A. ROBERT BELLOWS, M.D.
J. SIDNEY STILLMAN, M.D.
Boston, Massachusetts

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RAEDER'S SYNDROME

Editor:

The provocative paper "Raeder's paratrigeminal syndrome," by D. N. Cohen, Z. N. Zakov, V. D. Salanga, and D. F. Dohn (Am. J. Ophthalmol. 79:1044, 1975), brings up a semantic issue that has caused, and no doubt will continue to cause, confusion among ophthalmologists and their colleagues in other specialty areas. So-called Raeder's paratrigeminal syndrome of the benign type (Group 2) with periorbital pain and ipsilateral oculosympathetic paresis should properly be called "cluster headache." This latter term has become generally accepted by those who specialize in headache problems.[1-3] The benign nature of the process has been emphasized by many authors and is well reviewed by Cohen and associates. The term cluster headache has descriptive value because the symptoms and signs are thought to be of a vascular nature with a pathophysiology similar to that of migraine. By placing a "headache" label on such patients rather than a "syndrome" label, invasive diagnostic procedures are less likely to be invoked.

Use of the term Raeder's syndrome should probably be reserved for those cases with additional features of cranial nerve involvement or other findings that do merit definitive diagnostic evaluation. Over the years only three cases of aneurysm have been reported in association with the benign type of Raeder's syndrome (Group 2) as noted by Cohen and associates. Whether the aneurysm in those cases was the cause of the pain remains unclear. Surgery was not undertaken in any of the cases; one patient improved without treatment and no follow-up was provided in the other two cases.

More universal acceptance of the term cluster headache would serve to clear up eponymic confusion and put such cases in clearer perspective.

ROBERT E. CURRAN
Pawtucket, Rhode Island

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REPLY

Editor:

When there are clear-cut distinctions between the findings in two types of disease and when treatment is different for the two entities—the logical reason to "split" them from each other—we believe that Raeder's

syndrome falls within the latter category when compared to cluster headaches (histamine, cephalalgia, Horton's headache).

Cluster headaches imply just what their name infers, that is, the pains come in clusters and are severe. This type of pain generally occurs in men and in middle age. In its typical form it is likely to have its onset at night and waken the patient with severe spasms of head pain. The pain can be so severe that it can drive the patient to suicide. It can be an associated Horner's syndrome and usually the eye on the affected side is injected. The patient may also have swelling and mucous secretion from the nasal membranes on the affected side. This type of headache has responded favorably to medication used in the treatment of migraine headache and is also treated with histamine desensitization with some degree of efficacy. These headaches generally occur repeatedly from day to day for a period of time and they disappear for a year or more, only to recur. From the clinical description cluster headaches are apparently different in many ways from the pain associated with Group 2, Raeder's syndrome, as described in our paper and others.

While we feel that Raeder's paratrigeminal syndrome is a distinct entity from cluster headaches we agree with Dr. Curran that, in general, patients with the benign type of Raeder's syndrome should not have unnecessary and basic diagnostic procedures. We try to stress the point that the typical benign syndrome should not have invasive procedures while certain patients with atypical features of the disease stimulate more intensive diagnostic examination.

Doctor Curran was not correct in stating that surgery was not undertaken in any of the cases described in our paper. One patient (Case 2) underwent a surgical arterial anastomosis between the right superficial temporal artery and the right middle cerebral artery in an attempt to improve his cerebral circulation. Reading over our case history, however, this was misprinted in the published paper. The conclusion of the case report on page 1045 should read as follows: "In September 1972, the patient underwent surgical arterial anastomosis between the right superficial temporal artery and right middle cerebral artery." As a further follow-up in Case 1, one year and nine months after the patient was first seen she still has the same steady pain and the Horner's syndrome persists.

DAVID N. COHEN, M.D.
Z. NICHOLAS ZAKOV, M.D.
VIRGILIO D. SALANGA, M.D.
DONALD F. DOHN, M.D.
Cleveland, Ohio

CONTROLLED CLINICAL TRIALS IN THE TREATMENT OF MACULAR DISEASE

Editor:

Professor Jules François, in his response to Dr. Robert Frank's letter (Am. J. Ophthalmol. 80:161, 1975), states that controlled studies are "difficult and hazardous in the treatment of macular diseases, just as they are in diabetic retinopathy, because neither two eyes nor two cases are exactly the same and because the natural course differs from one case to another."

If it were possible to predict exactly the prognosis of an eye from the course of a fellow eye, from the status of a matched case, or from a predictable natural history, the need for carefully controlled studies would be obviated. The variable prognosis of chronic medical diseases led Hill[1] and others to develop the controlled clinical trial as a reliable method for evaluating therapy in these diseases. The hallmark of these clinical trials is the random assignment of patients to the treatment or control group. Although no two individuals are exactly comparable, randomization helps to assure the comparability of the treated and control groups both in known relevant factors and unknown factors. If the trial is then carried out with these randomly assigned groups and with care to avoid bias, as recently summarized by Ederer,[2] it is possible to evaluate treatment modalities in diseases with a variable natural history. This

evaluation allows us to predict the outcome for a group of patients even though we cannot predict the outcome in individuals. I fully agree with Professor François that such studies are difficult, but not to undertake them in areas of major importance is hazardous. As pointed out by Chalmers,[3] "It is more ethical to randomize a patient into either standard therapy or a new therapy, than it is to give the patient a new or the standard therapy as if we knew that one or the other was better, when either might actually be more harmful than beneficial." Unfortunately, past experience demonstrates all too clearly that enthusiasm for new treatment modalities, and patients who are anxious to get better, make the early subjective evaluations so biased as to be difficult if not impossible to interpret.

The personal experiences and subjective observations of individual investigators should lead the major university centers to cooperate in the careful evaluation of the promising treatment modalities so we can merge the art and science of medicine for the maximal benefit of our patients.

FREDERICK L. FERRIS III, M.D.
Baltimore, Maryland

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REPLY

Editor:

I agree with the comments of Dr. Ferris. Randomization, helping to assure the comparability of treated and control groups both in known relevant factors and unknown factors, is a progress in controlled studies. Nevertheless, these remain difficult, as Dr. Ferris agrees.

PROFESSOR J. FRANÇOIS
Ghent, Belgium

CORRECTIONS

In the article, "Perivascular and intervascular reticular fibers of the retina," by Norman Ashton and Ramesh Tripathi (Am. J. Ophthalmol. 80:337, 1975), Figure 10, center and bottom, were interchanged.

In the article, "A new mucolipidosis with psychomotor retardation, corneal clouding, and retinal degeneration," by Frank W. Newell, Reuben Matalon, and Steven Meyer (Am. J. Ophthalmol. 80:446, 1975), Figures 6 and 8 were interchanged.

BOOK REVIEWS

THE DEVELOPMENTAL NEUROPSYCHOLOGY OF SENSORY DEPRIVATION. Edited by Austin H. Riesen. Academic Press, Inc., 1975. Clothbound, 303 pages, table of contents, index, 40 black and white figures. $16.50

The effect of decreased or abnormally altered visual input on neural structure and function in visually immature animals has recently become an area of prime interest for visual scientists. Much information has accumulated during the last decade, most of it published in scientific journals not easily accessible to the clinically oriented ophthalmologist. This is regrettable, inasmuch as this work may eventually have far-reaching implications with respect to the treatment of strabismus, amblyopia, congenital cataracts, and corneal disease in children. We must be grateful, therefore, to Professor Riesen, and the other contributors to this book who have summarized the current knowledge on this subject. The anatomical, neurophysiological, neurochemical, electrophysiological, and behavioral changes that occur after decreased or enhanced stimulation of the visual system, are reviewed in nine chapters. Because of the nearly overwhelming amount of new data in this area during the past two to three years, an unavoidable shortcoming of a book of this type is that it is no longer current on the day of publication. Some of the authors'

conclusions and parts of their discussions must be modified in light of most recent information. Nevertheless, this book is indispensable for the visual scientist who will find a wealth of information and an excellent summary of the literature. Ophthalmologists whose interests in the visual system go beyond clinical ophthalmology will also find this book fascinating reading.

GUNTER K. VON NOORDEN

ADENINE ARABINOSIDE: AN ANTIVIRAL AGENT. Edited by Deborah Pavan-Langston, Robert A. Buchanan, and Charles A. Alford, Jr. New York, Raven Press, 1975. Clothbound, 425 pages, table of contents, index, 128 black and white figures. $21.50

This is a compilation of papers presented at a symposium in San Francisco on Sept. 16-17, 1974, and sponsored by Parke, Davis and Company. The subject of this symposium was one of the new antivirals, adenine arabinoside. The text avoids many of the pitfalls often seen in such symposium compilations in that the papers are authoritative, comprehensive, and provide excellent reviews of the area concerned in addition to the new information provided by individual authors. The text is understandable and easy to read.

The book is divided into three major sections. The first is concerned with preclinical studies and deals with the metabolism of adenine arabinoside, its activity in tissue culture against various herpes infections, its toxicology and animal pharmacology, and its teratogenicity and mutagenicity in animals. The chapters do not always follow each other in an obviously logical order, but the flow of information is smooth and there is minimal overlap in this extremely authoritative description.

The second area covered by the book is that of parenteral studies, beginning with a discussion of the human pharmacology of this drug, and describing the trials in man in severe progressive mucocutaneous herpes simplex, neonatal infections, varicella-zoster infections, cytomegalovirus, and smallpox infections, as well as some of the studies on cancer chemotherapy. Although projected double-blind parenteral studies are outlined, the drug is clearly ineffective in the therapy of smallpox, and, though it shows promise in the other areas, no sufficient control studies have been done to draw any definite conclusions. Evidence suggesting the parenteral efficacy of the drug in nonocular disease is presented, however, and the fact that the drug does not depress the immune response to the virus while it is being given is documented.

The final section of the book deals with the ophthalmic studies. Certainly the most important chapter in this section is that by Dresner and Seamans which summarizes the double-masked studies of idoxuridine as compared with adenine arabinoside. From these studies it is clear that the drugs are of comparable potency and appear to be of comparable toxicity. Papers in this section, however, document unequivocally that patients who are allergic or unresponsive to idoxuridine, or who have had a toxic reaction to idoxuridine, can be effectively treated with adenine arabinoside. In this section also is a summary of the double-masked study on parenteral adenine arabinoside, documenting the first effective treatment of deep herpetic keratouveitis by intravenous adenine arabinoside in controlled double-masked studies.

This volume is a valuable definitive summary of this particular antiviral compound.

HERBERT F. KAUFMAN

OPHTHALMIC NURSING. By Vera Darling and Margaret Thorpe. Baltimore, Williams and Wilkins Company, 1975. Paperbound, 195 pages, table of contents, index, 41 black and white figures. $6.25

This is a small paperback book written by two English nurses, organized into 16

chapters, nine of which deal with various anatomical structures of the eye, such as the lens, the retina, the cornea and sclera, and the like. These in turn can be considered as having three sections each: (1) anatomy of the structure, (2) few diseases affecting this structure, and (3) nursing care pertaining to these diseases. In addition, there are seven miscellaneous chapters, such as Procedures and Techniques, Medications and Eye Drops, Tropical Conditions, and Blindness.

The chapters dealing with the structures give a short but good review of the anatomy and physiology. The descriptions of the diseases listed are good, but the diseases do not appear to be selected on the basis of frequency or importance or to be listed in any rational order. For instance, the conditions listed in the chapter on the retina include central retinal vein and artery thrombosis, solar retinopathy, retinal detachment and retinoblastoma, but do not include diabetic retinopathy or hypertensive retinopathy. The chapter on the cornea omits all degenerative conditions, such as Fuchs' dystrophy or bullous keratopathy, yet mentions such an esoteric operation as eye-tooth transplant. Similarly, epidemic keratoconjunctivitis is described under Tropical Conditions along with onchocerciasis and Loa Loa.

The portions of the chapters dealing with surgical nursing care often appear not to apply to American conditions. For instance, England has socialized medicine which may prolong the length of the hospital stay. In many instances the authors indicate that a patient is admitted 48 hours before surgery for extensive work-up. This may not always be possible in the United States due to high costs of hospitals beds. Similarly, postoperative care varies widely from country to country and hospital to hospital, and the authors appear to describe conditions limited to their own institution. For instance, statements such as "the majority of operations are now carried out under a general anesthetic" may not hold true in many hospitals in the United States. Also, the postoperative schedules described may seem more restrictive than is customary in this country.

As with the surgical nursing care, the chapters dealing with procedures and techniques, medications and eye drops, and blindness are interesting to read, but not necessarily relevant to practices in this country. For instance, hot spoon bathing or instillation of eye ointment with a glass rod are procedures generally not used here, and some other procedures—for example, subconjunc-

jamin F. Boyd. Panama, R.P., Pan

ulcers—are usually carried out by a doctor.

Despite some of the differences in nursing care between the two countries, this book is well worth reading. The sections on anatomy, and the descriptions of the listed diseases provide a good introduction to ophthalmology. Although the description of specific nursing procedures and schedules may be of limited value, the general philosophy of what eye nursing should be is excellent. The authors have a thorough knowledge of their field and have managed to impart this information well. All nursing personnel dealing with ophthalmic patients would benefit from reading it.

MAIJA UOTILA

HIGHLIGHTS OF OPHTHALMOLOGY. By Benjamin F. Boyd. Panama, R. P., Pan American Institute of Ophthalmology, 1975-1976. Clothbound, 625 pages, table of contents, index, over 200 black and white figures. $39.50

During the past 16 years Boyd has established an unusual and personal format of personal interviews providing some 16 annual volumes concerning most recent advances in ophthalmology. He follows closely those meetings attracting the most innovative and active clinicians and laboratory workers. He then arranges a formal tape-recorded interview in which he develops a give-and-take series of questions and answers that are combined with illustrations by the remarkably

talented Indian artist, Luis Mendez, of the Clinica Boyd.

The result is an interesting volume with a broad spectrum of topics bringing out recent material that is not always destined for adoption but rather reflects the current viewpoints of outstanding practitioners and investigators working in the forefront of ophthalmic advances. The current edition presents much detail, described so that one senses he is overhearing two superbly trained teachers discussing a subject of mutual interest.

Many topics are considered: diabetic retinopathy with Patz, Spalter, Dellaporta, and L'Esperance: retinitis pigmentosa with Hussels-Maumenee; strabismus with von Noorden, Veronneau-Troutman, Folk, Elliot, Tabor, and Diorio; ocular inflammation with Henry F. Allen and Sears; keratoplasty with Ainslie; cataract incision with Troutman, Paton, and Ryan; phacoemulsification with Praeger, Paton, and Emery; intraocular lens implant with Drews, Worst, Binkhorst, Jaffe, and Choyce; contact lenses with Halberg; pterygium with Moreno and Pinkerton; and glaucoma with Odeh-Nasrala, Kirsch, Anderson, Podos, Maumenee, Luntz, Sampaolesi, Sears, Armaly, Richardson, and Swan.

The combination of interviews with authoritative individuals and Boyd's searching questions and fine illustrations makes this volume a useful way to keep up with modern thinking in ophthalmology.

FRANK W. NEWELL

FIRST INTERNATIONAL SYMPOSIUM ON ARTIFICIAL LENS IMPLANTATION, UTRECHT—APRIL 1974. Edited by A. Th. M. van Balen. The Netherlands, Dr. W. Junk, 1975. Paperbound, 169 pages, table of contents, 15 tables, 120 black and white figures. $20.63

This group of papers presented at the First International Symposium on Artificial Lens Implantation, April 27, 1974, at Utrecht, The Netherlands, marked an important event in ophthalmology. The occasion was the presentation of the Snellen Medal to Cornelius D. Binkhorst of The Netherlands. In 1958, on the centennial of the Koninklijk Nederlands Gasthuis voor Ooglijders (Royal Dutch Eye Hospital) at Utrecht, the Snellen Medal was founded by the board of the hospital in memory of Professor Herman Snellen, Sr. It was decreed that it should be presented each fifth year to a person of Dutch nationality who had exceptionally distinguished himself in the field of ophthalmology. The Snellen committee was unanimous in their choice of laureate of this award. Dr. Hoppenbrouwers, the committee chairman, invited three foreign authorities on lens implant to participate in the proceedings, thus providing an international flavor. They were Draeger and Gernet of West Germany and Jaffe of the United States.

Van Balen of Rotterdam discussed lens implants in children with traumatic cataracts. Twenty-four of 37 eyes attained a visual acuity of 0.5 or better with a high percentage of binocular vision. Discissions were required in 60% of these eyes and more than once in half. Although we still do not know whether the iridocapsular (not the iris-clip) lens is tolerated more than ten years in an eye, van Balen advised implantation of this lens in unilateral traumatic cataract in children because no other method of correction of unilateral aphakia in children is satisfactory in the prevention of amblyopia and the preservation of binocular vision.

Leeman of Amersfoort reported 100 cases of intracapsular lens extraction with implantation of an iris-clip lens with excellent results. He observed there was almost no difference in the incidence of cystoid macular edema with and without an implant after intracapsular lens extraction. In four eyes, in the implant group and in three eyes in a control group, visual acuity was reduced to between 5/15 and 5/30.

Gernet of Münster discussed ultrasonic

biometry and optics. Unfortunately, his report was reduced to a small abstract. Nordlohne of Vlissingen presented data supportive of Binkhorst's view that an iridocapsular lens after an extracapsular extraction has some advantages over an iris-clip lens with an intracapsular extraction with regard to the incidence of postoperative corneal edema and dislocation. Manschot of Rotterdam reported that only one eye (containing an iridocapsular lens) had to be enucleated of 2,724 eyes in which Binkhorst lenses were implanted before 1972.

Jaffe reviewed the current status of intraocular lenses in the United States and described some of his personal experiences and his conservative approach to indications. Draeger of Bremen discussed his use of the surgical microscope. Worst's contributions included technique and lens design. His superbly presented thoughts alone make the volume useful. Binkhorst reviewed his long involvement with implant surgery and the reasons for the evolution of his present methods. His attention to meticulous detail and his objective reasoning will impress every reader.

The reader will thoroughly enjoy the 28 pages devoted to panel discussion, replete with facts, opinions, and humor. The most disappointing aspect was the omission of the touching text of the Snellen Medal presentation.

NORMAN S. JAFFE

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

ARCHIVES OF OPHTHALMOLOGY

PILOCARPINE OCUSERTS. Quigley, H. A., Pollack, I. P., and Harbin, T. S., Jr. (Wilmer Inst., Johns Hopkins Hosp., Baltimore, Md.). Arch. Ophthalmol. 93: 771, 1975.

The weaker Ocusert P-20 was found to be equivalent to about ½% or 1% pilocarpine, while the stronger Ocusert which releases 40 μg/hr controls eyes requiring 2 and 4% pilocarpine. However, some eyes which were controlled with 4% pilocarpine were not controlled by the P-40 Ocusert alone and epinephrine drops had to be used as well. There was a definite decline in the release of pilocarpine from the Ocusert at the end of seven days and therefore it is recommended that these devices be used only for a seven day period. In a group of 22 patients Ocuserts were successfully worn for extended periods by 80% of the group with good pressure control and no loss of visual field during a one year period. (5 figures, 1 table, 6 references)—David Shoch

BRAIN

VISUAL EVOKED RESPONSES IN THE DIAGNOSIS AND MANAGEMENT OF PATIENTS SUSPECTED OF MULTIPLE SCLEROSIS. Asselman, J., Chadwick, S. W., and Marsden, C. D. (Univ. Dept. Neurol., Inst. Psychiatry, London). Brain 98:261, 1975.

A prolonged latency to the peak of the major positive potential in the VER recorded to pattern reversal is a very sensitive method of detecting optic nerve damage, whatever its cause (provided local ocular disease is excluded). The test may detect abnormality when none is apparent on clinical examination, and provides a potential means of establishing the presence of multiple lesions in the nervous system in those suspected of multiple sclerosis. (12 figures, 4 tables, 11 references)—Authors' abstract

USE OF THE PULFRICH PENDULUM FOR DETECTING ABNORMAL DELAY IN THE VISUAL PATHWAY IN MULTIPLE SCLEROSIS. Rushton, D. (Dept. Neurol., Inst. Psychiatry, London). Brain 98:283, 1975.

Patients with different conductive velocities in their two optic nerves perceive a pendulum which is swinging in a straight line as pursuing an elliptical path. This effect is difficult to demonstrate with a real pendulum because of interference by other clues to depth movement, such as size of retinal image and accommodative effort. It was therefore necessary to produce the effect with two oscilloscopes viewed through a stereopticon-like device. The test was positive in some patients with multiple sclerosis but was not as sensitive as the VER. Compared with the latter, Pulfrich's pendulum suffers from the disadvantages of requiring co-operation, binocular vision, and unequal damage to the optic nerves. (7 figures, 2 tables, 12 references)—Joel G. Sacks

THE CEREBRAL PATHWAYS OF OPTOKINETIC NYSTAGMUS: A NEURO-ANATOMICAL STUDY. Blackwood, W., Dix, M. R., and Rudge, P. (Inst. Neurology, National Hosp., London). Brain 98:297, 1975.

Abnormalities of optokinetic nystagmus are described in a patient with pathologically proven bilateral infarcts in the middle cerebral artery territories. There were no other central nervous system lesions. These abnormalities of eye movement are interpreted as indicating an inhibitory effect of the frontal eye fields upon the occipital lobes. (14 figures, 18 references)—Authors' abstract

BRITISH MEDICAL JOURNAL

UNTOWARD EFFECTS ASSOCIATED WITH PRACTOLOL ADMINISTRATION: OCULOMUCOCUTANEOUS SYNDROME. Wright, P. (Moorfields Eye Hosp. and King's College Hosp., London). Br. Med. J. 1:595, 1975.

Keratoconjunctivitis sicca, conjunctival scarring, fibrosis, metaplasia, and shrinkage developed in 27 patients as an adverse reaction to practolol. Rashes, nasal and mucosal ulceration, fibrous or plastic peritonitis, pleurisy, cochlear

damage, and secretory otitis media also occurred in some cases. Three patients suffered profound visual loss though most retained good vision. Symptoms and signs improved on withdrawal of the drug, but reduction of tear secretion persisted in most patients. (7 figures, 1 table, 6 references)—Author's abstract

Experimental Eye Research

ENDOTHELIAL WOUND REPAIR IN PRIMATE CORNEA. Van Horn, D. L., and Hyndiuk, R. A. (Depts. Ophthalmol. and Physiology, Med. College Wis., Milwaukee, Wis.). Exp. Eye Res. 21:113, 1975.

A light and electron microscopic study of the regeneration of corneal endothelial cells after transcorneal cryo-destruction in monkeys shows migration and enlargement of the remaining healthy peripheral endothelial cells to cover the defect. There was no evidence of an increase in endothelial cell population by cellular division. There was an increase in cytoplasmic organelles indicating an attempt by the cells to be more active in metabolic dehydrating of the stroma. Corneal thickness decreased from its greatest thickness, which occurred with edema from the absence of endothelium, toward normal suggesting that the enlarged cells were able to increase their metabolic activity; but failure to return to normal thickness indicated that this mechanism was only partially effective. (14 figures, 20 references)—Barton L. Hodes

THE EFFECT OF ACETYLCHOLINE AND ESERINE ON THE MOVEMENT OF Na^+ ACROSS THE CORNEAL EPITHELIUM. Stevenson, R. W., and Wilson, W. S. (National Inst. for Biological Standards and Control, Holly Hill, London). Exp. Eye Res. 21:235, 1975.

The fact that the corneal epithelium contains one of the highest concentrations of acetylcholine (ACh) in the body, far in excess of that which is necessary for the mediation of sensation, coupled with the knowledge that ACh influences membrane permeability to Na^+ in other tissues of the body, led the authors to explore the possibility of an active epithelial Na^+ "pump" which contributes to corneal hydration and transparency. Exogenous ACh caused stromal Na^+ to decrease, while pretreatment with an ACh inhibitor caused a marked increase in stromal Na^+. (5 figures, 1 table, 35 references)—Barton L. Hodes

PILOCARPINE LEVELS IN THE EYES OF RABBITS FOLLOWING TOPICAL APPLICATION. Lazare, R., and Horlington, M. (Smith and Nephew Research Limited, Harlow, England). Exp. Eye Res. 21:281, 1975.

Tritium-labelled pilocarpine nitrate or hydrochloride was instilled into the conjunctival sac of several strains of rabbit in an effort to determine the time-related concentration of this drug in cornea, aqueous, and iris and correlate it with the pharmacologic action of the drug. Drug was present in highest concentration in the cornea seven minutes after instillation; it was present in low concentration in aqueous and iris at this time. Corneal drug levels decreased rapidly and were accompanied by simultaneous aqueous and iris level increases to a maximum at 20 minutes. From this point on, all three loci of pilocarpine showed a steady rate of decline. (1 figure, 4 tables, 9 references)—Barton L. Hodes

MOLECULAR SIEVE EFFECT OF THE BLOOD-AQUEOUS BARRIER. Dernouchamps, J. P., and Heremans, J. F. (Dept. Ophthalmol., Université Catholique de Louvain, Louvain, Belgium). Exp. Eye Res. 21:289, 1975.

The pore size of the blood-aqueous barrier is proposed to be 104 Angstrom units. This thesis is based upon the relative concentrations of seven plasma proteins in aqueous and plasma (AH/S concentration ratio), their molecular weights, and their "molecular diffusion radius" expressed in Angstrom units. (2 figures, 4 tables, 18 references)—Barton L. Hodes

Investigative Ophthalmology

LOCAL GRAFT VERSUS HOST REACTIONS WITHIN THE ANTERIOR CHAMBER OF THE EYE: THE FORMATION OF CORNEAL ENDOTHELIAL POCKS. Khodadoust, A. A., and Silverstein, A. M. (Wilmer Inst., Johns Hopkins Univ. School Med., Baltimore, Md.). Invest. Ophthalmol. 14:640, 1975.

In an effort to prove that the graft versus host (GVH) immune reaction is mediated on

a cellular (sensitized lymphocyte) basis, full thickness skin taken from one adult albino rabbit was grafted to another to "presensitize" the recipient to the donor's tissues. A suspension of lymphocytes, harvested from the recipient's preauricular node on the day following rejection of the donor's skin, was injected into the anterior chamber of one eye of the donor, the recipient, and a third immunologically uninvolved rabbit. The resulting uveitic process was followed and graded, and the animals sacrificed at intervals. The eyes were enucleated and flat mounts of the endothelium were prepared. Endothelial cell destruction was evidenced in the original donor eyes and, to a lesser degree, in the third animal; but the mild uveitis experienced by the sensitized recipient whose own lymphocytes were injected into his own anterior chamber, was accompanied by no histologic evidence of endothelial cell destruction. (5 figures, 15 references)—Barton L. Hodes

HISTOLOGY OF THE MONKEY LATERAL GENICULATE NUCLEUS AFTER UNILATERAL LID CLOSURE AND EXPERIMENTAL STRABISMUS: FURTHER OBSERVATIONS. von Noorden, G. K., and Middleditch, P. R. (Dept. Ophthalmol., Baylor College Med., Houston, Tex.). Invest. Ophthalmol. 14: 674, 1975.

Experimentally produced amblyopia, both of the strabismic and deprivation variety, was accompanied by histologic evidence of shrinkage of all cell layers in the lateral geniculate nucleus. The severity of this shrinkage correlated well with the clinical impression of the severity of the amblyopia; little shrinkage was found in animals who had developed an alternating exotropia. (4 figures, 2 tables, 26 references)—Barton L. Hodes

ADENOSINE 3′.5′-MONOPHOSPHATE ANALOGUE INCREASES THE OUTFLOW FACILITY OF THE PRIMATE EYE. Neufeld, A. H., and Sears, M. L. (Dept. Ophthalmol., Yale Univ. School of Med., New Haven, Conn.). Invest. Ophthalmol. 14:688, 1975.

Perfusion of one eye of anesthetized vervet monkeys with 8-methylthio cyclic-AMP (SQ 30,002) resulted in a doubling of the facility of outflow when compared with the fellow eye which was perfused with an artificial aqueous humor. The response of the eye to perfusion with the potent analogue of cyclic-AMP is cited as evidence that the adrenergic control of aqueous outflow is at least in part mediated by cyclic-AMP. It is hypothesized that agents which can stimulate the production of cyclic-AMP or potentiate its action may prove effective in the treatment of chronic simple glaucoma. (1 table, 10 references)—Barton L. Hodes

SPECIALIZATIONS OF THE RETINOCHOROIDAL JUNCTURE. Miki, H., Bellhorn, M.B., and Henkind, P. (Dept. Ophthalmol., Albert Einstein College Med., Bronx, N.Y.). Invest. Ophthalmol. 14:701, 1975.

This transmission electron microscopic study shows the presence of firm attachment sites along basal invaginations of the retinal pigment epithelial (RPE) cells which resemble the hemidesmosomes which bind the basal plasma membrane of the RPE cells to Bruch's membrane. They apparently play a role in maintaining adhesion between the RPE and Bruch's membrane. (4 figures, 7 references)—Barton L. Hodes

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

LIMITED FORM OF WEGENER GRANULOMATOSIS: EYE INVOLVEMENT AS A MAJOR SIGN. Coutu, R. E., Klein, M., Lessell, S., Friedman, E., and Snider, G. L. (Depts. Med. and Ophthalmol., Boston Univ. School Med., Boston, Mass.). J.A.M.A. 233:868, 1975.

Bilateral uveitis was the initial manifestation of a limited form of Wegener granulomatosis in a 47-year-old man. Diagnosis was established by biopsy of a pulmonary nodule. Subsequently, evidence of lesions developed in the patient's central and peripheral nervous systems, but renal lesions were absent. Pulmonary lesions regressed on therapy with azathioprine and prednisone. Blindness ultimately resulted from retinal phlebitis, vitreous hemorrhages, and neovascular glaucoma. (5 figures, 13 references)—Authors' abstract

JOURNAL OF CLINICAL ULTRASOUND

A METHOD FOR SPECTRA-COLOR B-SCAN ULTRASONOGRAPHY. Holasek, E., Gans,

L. A., Purnell, E. W., and Sokollu, A. (Div. Ophthalmol., Case Western Reserve University, Cleveland, Ohio). J. Clin. Ultrasound 3:175, 1975.

Spectra-Color Ultrasonography (S.C.U.) is a new technique investigated for increasing the information obtainable from B-scan ultrasonography of the eye and orbit. A wide band transducer is used and its signals are separated into three narrower bands; each band is then represented by one of the three primary colors. A single full sector scan is taken with each color filter and all three sector scans are photographed on a single frame of color film resulting in a "triple exposure." Tissue characterization and identification are still under investigation. (5 figures, 2 references)—Barton L. Hodes

Klinische Monatsblätter für Augenheilkunde

MALIGNANT COURSE OF BASAL CELL CARCINOMAS OF THE LID. (German) Brewitt, H., and Huerkamp, B. (Eye Clinic, Hannover, West Germany). Klin. Monatsbl. Augenheilkd. 166:770, 1975.

Although basal cell carcinomas of the lid are known to be only locally malignant, they can extend if not treated and result in rather severe consequences. Three such cases are presented here. In the first case there was destruction of the eyelids from neglect of treatment. In the second, the destruction extended to the orbit and nearby sinuses while in the third case there was actual infiltration of the brain. The authors, therefore, emphasize that these lesions should not be treated lightly but early active treatment is indicated. They further make a plea for histologic examination of all specimens to make sure that the entire lesion has been removed. (6 figures, 7 references)—David Shoch

LASER MICROSURGERY IN GLAUCOMA. (German) Hager, H. (Steglitz Clinic, Berlin, Germany). Klin. Monatsbl. Augenheilkd. 167:18, 1975.

The coagulation of the iris base was quite effective in the treatment of angle closure glaucoma. Of 45 patients so treated 14 were compensated without miotics and 16 with the use of miotics for a total of 30 out of the 45. However, in open angle glaucoma of 32 patients only eight were felt to be compensated by the laser microsurgery with or without the use of miotics. In a second group of patients of 28 patients where trabecular puncture was done, ten of the 28 were controlled with or without miotics after the treatment. (7 figures, 3 tables, 29 references)—David Shoch

CLINICAL AND EXPERIMENTAL INVESTIGATION OF A NON-CONTACT TONOMETER. (German) Draeger, J., Jessen, K., and Haselmann, G. (Eye Clinic, Central Hosp., Bremen, Germany). Klin. Monatsbl. Augenheilkd. 167:27, 1975.

Comparative measurements were made on 462 patients with a non-contact tonometer and a hand applanation tonometer. In this group were patients with normal and with elevated intraocular pressure. The standard deviation for patients with normal intraocular pressure was ± 6.52 mm Hg and for those with elevated intraocular pressure ± 13.2 mm Hg. This indicates less reliability of the non-contact tonometer as compared with conventional applanation or even Schiotz-tonometers. The inability to read the tension when the corneal surface is rough is a marked disadvantage for clinical use of non-contact tonometers. (11 figures, 1 table, 4 references)—David Shoch

LONG-TERM RESULTS OF LASER-TRABECULAR-PUNCTURE. (German) Fechner, P. U., Teichmann, I., and Teichmann, K. D. (Robert Koch Hosp., Hannover, Germany). Klin. Monatsbl. Augenheilkd. 167:102, 1975.

Thirty-eight eyes with open angle glaucoma that were treated by laser-trabecular-puncture were examined two years after treatment. In only three of the 38 eyes was the intraocular pressure lowered. Gonioscopy showed that the pores made by the laser had become occluded by scar tissue and goniosynechiae. (2 figures, 6 references)—David Shoch

RETINOBLASTOMA IN AN ADULT. (German) Kremlicka, L., and Roubkova, H.

(Prague, Czechoslovakia). Klin. Monatsbl. Augenheilkd. 167:119, 1975.

A rare case of late occurrence of retinoblastoma in a 42-year-old man is described. This diagnosis is always made with difficulty in an adult and the authors simply point out that we must be aware of the fact that although retinoblastoma is most commonly a disease of infants, it has been reported in adults on numerous occasions. (4 figures, 16 references)—David Shoch

EXPERIENCES WITH THE NON-CONTACT-TONOMETER. (German) Dittmar, P., Weinberg, M., and Liegl, O. (State Hosp., Berlin, Germany). Klin. Monatsbl. Augenheilkd. 167:137, 1975.

The non-contact-tonometer (American Optical Company) is simple to use and the intraocular pressure can be measured without any manipulation of the eye. However, the measurements are only possible with smooth corneas. In addition, the results obtained are not as exact as those of the traditional methods. Finally, there is at this time no mechanism for standardization of this new tonometer. (3 figures, 1 table, 3 references)—David Shoch

NEUROLOGY

A FAMILY WITH COEXISTENT VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS AND VON HIPPEL-LINDAU'S DISEASE. Tishler, P. V. (Dept. Med., Harvard Med. School, Boston, Mass.). Neurology 25:840, 1975.

A large kindred has two coexistent neurocutaneous syndromes. Certain members appear to have von Recklinghausen's neurofibromatosis (cutaneous neurofibromata, café-au-lait spots), others have von Hippel-Lindau's disease (angiomatosis retinae, renal cell carcinomas, pancreatic cysts), and at least one individual has a combined syndrome (neurofibromata, café-au-lait spots, pheochromocytomas, cerebellar hemangioblastoma, renal cell carcinoma, pancreatic cysts). Inheritance may be through either two separate genes segregating coincidentally in this family, or a unique single gene with pleiotropic expressivity. (1 figure, 12 references)—Author's abstract

NEW ENGLAND JOURNAL OF MEDICINE

A PRACTICAL CHROMOGENIC PROCEDURE FOR THE DETECTION OF HOMOZYGOTES AND HETEROZYGOUS CARRIERS OF NIEMANN-PICK DISEASE. Gal, A. E., Brady, R. O., Hibbert, S. R., and Pentchev, P. G. (National Institutes of Health, Bethesda, Md.). N. Engl. J. Med. 293:632, 1975.

Niemann-Pick disease is caused by a deficiency of sphingomyelinase in organs and tissues. It has been possible to determine the level of this enzyme in organs and tissues of carriers by the use of a rather expensive and time consuming radioactive method. The authors have devised a new technique using an analogue of sphingomyelin and this substance is hydrolyzable by sphingomyelinase from extracts of human liver tissue, cultured skin fibroblasts, cultured amniotic cells, and washed leukocyte preparations. The resultant compound is chromogenic and the level of sphingomyelinase can be determined. Thus a rapid facile method has been developed which will eliminate the previous requirement for radiocarbon-labeled sphingomyelin for these tests. It has already been shown to be reliable for the detection of a Niemann-Pick heterozygote in utero and therefore should be a useful substrate for the prenatal diagnosis of the disease. (3 figures, 2 tables, 11 references)—David Shoch

OPHTHALMOLOGICA

FARNSWORTH 100-HUE TEST IN DIAGNOSIS OF ETHAMBUTOL-INDUCED DAMAGE TO OPTIC NERVE. Trusiewicz, D. (Dept. Ophthalmol., Central Railway Hospital, Warsaw, Poland). Ophthalmologica 171:425, 1975.

In patients treated with ethambutol, disturbances in color vision may be the first and only symptoms of the onset of toxic damage to the optic nerves. The Farnsworth 100-Hue test is especially suitable for examination of acquired disturbances in color vision. The technique is simple and the interpretation of the result which is presented both graphically and numerically is simple to interpret. The fact that the examination can be carried out by an auxiliary staff member represents another advantage of this test. (3 tables, 7 references)—David Shoch

Vision Research

THE SITES OF GENERATION OF EARLY AND LATE RECEPTOR POTENTIALS IN RODS. Govardovskiĭ, V. I. (Inst. Evolutionary Physiol. and Biochem., Leningrad, U.S.S.R.). Vision Res. 15:973, 1975.

At oblique illuminations of the retina cone ERP is maximal when light is polarized in the plane of the disks. Rod ERP is maximal when light is polarized along the photoreceptor axis, perpendicular to the disk plane. This means that the cone ERP is generated by the disks, and that the rods generate ERP due to the absorption of light by the rhodopsin molecules enclosed within the envelope membrane of the outer segment. Both the b-wave of electroretinogram and rod late receptor potential are generated due to the absorption of light by the disk membranes. There is no sign of the electrical coupling between the rod disks and the outer plasmic membrane, and physiological response is transmitted to this membrane from the site of photon absorption by means of some non-electrical process. (7 figures, 35 references)—Author's abstract

OPHTHALMIC MINIATURE

It begins to look, more and more disturbingly, as if the gift of language is the single human trait that marks us all genetically, setting us apart from all the rest of life. Language is, like nest-building or hive-making, the universal and biologically specific activity of human beings. We engage in it communally, compulsively, and automatically. We cannot be human without it; if we were to be separated from it our minds would die, as surely as bees lost from the hive.

Lewis Thomas, *The Lives of a Cell. Notes of a Biology Watcher*
Viking Press, 1974

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received at least three months prior to the date of occurrence.

JOHNS HOPKINS UNIVERSITY: CENTENNIAL CONGRESS ON RETINAL DISEASES

To celebrate the 100th anniversary of the founding of Johns Hopkins University, a Centennial Congress will be held in Baltimore, Sept. 20-23, 1976. The congress topics will be devoted to advances in retinal and choroidal diseases. For further information, write Arnall Patz, M.D., Room 155, Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, MD 21205.

JULES STEIN LECTURE AND SEMINAR

The Seventh Annual Jules Stein Lecture and Postgraduate Seminar will be presented at the Beverly Hilton Hotel, Los Angeles, California, April 23 and 24, 1976. The seminar topic for the meeting is "Pediatric Ophthalmology—A Current Review." The Jules Stein Lecture will be delivered by Frank W. Newell. The program co-chairmen are Arthur L. Rosenbaum and Leonard Apt. For further information, write Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, CA 90024.

FIGHT FOR SIGHT, INC.: TRAVEL GRANTS

The Fight for Sight announces that through a grant from the House of Vision, approximately 20 residents in ophthalmology having a minimum of one year's training may receive travel support of $300 to $500. The awards are intended to assist residents who are authors or coauthors of a paper to be presented at a scientific meeting or to participate in a symposium or seminar to which the candidate can make a significant contribution. Application forms are available from the Secretary, Fight for Sight, Inc., 41 W. 57th St., New York, NY 10019. The closing date for receipt of completed requests is Feb. 1, 1976.

EYE FOUNDATION OF AMERICA MEETING

The Eye Foundation of America will sponsor a meeting on ocular infections and their therapy April 2 and 3, 1976, in New Orleans. For further information, write George M. Haik, M.D., 1542 Tulane Ave., New Orleans, LA 70112.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY: ANNUAL MEETING

The Oregon Academy of Ophthalmology and Otolaryngology will hold its 35th annual postgraduate convention at the Sheraton Motor Inn, Portland, March 12 and 13, 1976.

Guest speakers for the ophthalmology section are G. Richard O'Connor, Stephen J. Ryan, T. F. Schlaegel, Jr., and Jerry A. Shields. The local faculty will consist of staff members of the University of Oregon Medical Sciences Center and Devers Eye Clinic. The fee for the meeting is $90 if paid by March 6, 1976; $100 thereafter. This includes lunch both days and the reception-banquet. Residents are admitted without charge on presentation of a qualifying letter from their respective department heads. The course is approved for continuing medical education credits under the accreditation program of the American Medical Association. For further information, write Miss Rebecca Tarshis, Executive Secretary, 918 N.E. 44th Ave., Portland, OR 97213.

UNIVERSITY OF TENNESSEE: ALUMNI RESIDENTS DAY

The Fifth Annual University of Tennessee Alumni Residents Day will be held at the university's College of Medicine in Memphis, March 4, 1976. For further information, write the University of Tennessee College of Medicine, Department of Ophthalmology, 858 Madison Ave., Memphis, TN 38163.

COLORADO OPHTHALMOLOGICAL SOCIETY: MIDWINTER MEETING

The Colorado Ophthalmological Society will hold its Fifth Annual Midwinter Meeting Jan. 25-30, 1976, at the Silver Tree/El Dorado Lodge, Snowmass Resort, Aspen, Colorado. For further information, write James R. Cerasoli, M.D., Program Chairman, Colorado Ophthalmological Society, 1601 E. 19th Ave., Denver, CO 80218.

UNIVERSITY OF FLORIDA: MIDWINTER SEMINAR IN OPHTHALMOLOGY AND OTOLARYNGOLOGY

The University of Florida College of Medicine, the University of Miami School of Medicine, and

the University of South Florida College of Medicine will hold their 30th annual seminar in ophthalmology and otolaryngology at the Americana Hotel, Miami Beach, Feb. 2-7, 1976. The program is approved for 30 credit hours by the Florida Medical Association. It is accredited by the Council on Medical Education and is acceptable for creditation toward the Physicians Recognition Awards. For additional information, write Michael I. O'Connor, Florida Midwinter Seminar, 428 E. Preston St., Baltimore, MD 21202.

San Antonio Ophthalmology and Otolaryngology Society: Annual Symposium

The San Antonio Ophthalmology and Otolaryngology Society will hold an Annual Symposium, "Glaucoma: Current Clinical Concepts," Feb. 28, 1976. Speakers are Steven M. Podos and Douglas R. Anderson. For further information, write Paul Cutler, M.D., Associate Dean for Continuing Medical Education, 7703 Floyd Curl Dr., San Antonio, TX 78284.

Manhattan Eye, Ear and Throat Hospital: Clinical Course

The Manhattan Eye, Ear and Throat Hospital will hold a course, "Contact B-scan Ultrasonography for the Clinician," Feb. 20 and 21, 1976. The course will include the basics of ultrasonography in ophthalmology and the application of contact, real-time B-scan ultrasonography for the practicing clinician. The course will be limited to 20 participants. For further information, write Yale Fisher, M.D., Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021.

University of Chicago Annual Alumni Day

The Annual Alumni Day of the University of Chicago will be held March 3, 1976. A. Edward Maumenee is the guest of honor. For further information, write Peter H. Morse, M.D., Department of Ophthalmology, 950 E. 59th St., Chicago, IL 60637.

Long Beach University Memorial Hospital Medical Center: Program on Neuro-ophthalmology

The Memorial Hospital Medical Center of Long Beach University of California, Irvine Center for Health Education, will hold a program on neuro-ophthalmology March 12 and 13, 1976. This will be a practical course for clinicians with emphasis on recognition, differential diagnosis, and management of common neuro-ophthalmic problems. Tuition is $125; $25 for residents and fellows in training. For further information, write Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach, CA 90801.

State University of New York, Downstate Medical Center: Ophthalmic Microsurgery Courses

The State University of New York, Downstate Medical Center, Brooklyn, will hold two intensive courses in microsurgery. The basic course will be held March 18-20, 1976. The advance course will be held March 22-24, 1976. The fee for each course will be $500, which includes all instructional materials (except instruments), transportation to and from the university, and luncheons. For further information, write Mrs. Sylvia Baer, Division of Ophthalmology, State University of New York, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY 11203.

Association for Research in Vision and Ophthalmology: Board of Trustees 1975-1976

The Board of Trustees for the Association for Research in Vision and Ophthalmology are: Herbert E. Kaufman, Abraham Spector, Lorrin A. Riggs, Bernard Schwartz, Adolph Cohen, James H. Elliott, John Lott Brown, David M. Maurice, Melvin L. Rubin, Claies H. Dohlman, and Gunter K. von Noorden.

The next meeting of the Association will take place in Sarasota, Florida, April 26-30, 1976.

Personal

Deborah Pavan-Langston

Deborah Pavan-Langston received the $25,000 Research to Prevent Blindness—William Friedkin Scholars Award for her research toward the development of Ara-AMP, a monophosphate ester of vidarabine, designed to attack deep-seated infections from two common, devastating types of herpes virus. Dr. Langston reported on her work with Ara-AMP at the April 1975 meeting of the Association for Research in Vision and Ophthalmology. The Scholars Award will permit her to begin human trials of the drug.

FIVE-YEAR OPHTHALMIC MEETING CALENDAR

For listings, write Bruce E. Spivey, M.D., Professor and Chairman, Pacific Medical Center, Department of Ophthalmology, P.O. Box 7999, San Francisco, CA 94120.

1976

JANUARY	4-6	VI Afro-Asian Congress of Ophthalmology	Madras, India
	6-15	Dedication, new facilities, Bascom Palmer Eye Institute	Miami
	17	American Board of Ophthalmology (written)	Multiple sites
		Ophthalmic Knowledge Assessment Program, AAOO (written)	Multiple sites
MARCH	24-26	The Czechoslovak Ophthalmological Society	Prague, Czechoslovakia
APRIL	5-9	European Congress of Ophthalmology	Hamburg, Germany
	26-30	Association for Research in Vision and Ophthalmology	Sarasota, Florida
	28-MAY 1	II World Congress on the Cornea	Washington, D.C.
MAY	7-10	American Board of Ophthalmology (oral)	Philadelphia
	14-16	American Ophthalmological Society	Kamuela, Hawaii
	16-21	Pacific Coast Oto-Ophthalmological Society	Seattle
JUNE	13-19	Club Jules Gonin Meeting	Lausanne, Switzerland
	26-JULY 1	American Medical Association, Annual Convention	Dallas
AUGUST	8-13	Asia Pacific Academy of Ophthalmology	Denpasar, Bali, Indonesia
OCTOBER	6-10	American Academy of Ophthalmology and Otolaryngology	Las Vegas
	11-15	American College of Surgeons, Clinical Congress	Chicago
	21-24	American Board of Ophthalmology (oral)	San Francisco
NOVEMBER	11-15	Association of American Medical Colleges	San Francisco
DECEMBER	2-5	American Board of Ophthalmology (oral)	Chicago
	4-8	American Medical Association, Clinical Convention	Philadelphia

1977

MARCH	20-25	XI Pan American Congress of Ophthalmology	Santiago, Chile
APRIL	24-28	Pacific Coast Oto-Ophthalmological Society	Tucson, Arizona
	26-30	Association for Research in Vision and Ophthalmology	Sarasota, Florida
MAY	4-7	American Board of Ophthalmology (oral)	San Francisco
	15-20	Instituto Barraquer VII International Course	Barcelona
	30-JUNE 1	American Ophthalmological Society	Hot Springs, Virginia
JUNE	18-23	American Medical Association Annual Convention	San Francisco
SEPTEMBER	10-11	International Intra-ocular Implant Society	Coronado, California
	25-OCT. 8	American Academy of Ophthalmology and Otolaryngology	Dallas (tentative)
OCTOBER	16-19	American Board of Ophthalmology (oral)	Philadelphia
	17-21	American College of Surgeons Clinical Congress	Dallas
NOVEMBER	6-10	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Washington, D.C.
DECEMBER	4-7	American Medical Association, Clinical Convention	Chicago

1978

APRIL	23-26	American Board of Ophthalmology (oral)	Philadelphia
MAY	14-21	International Congress of Ophthalmology—Concilium Ophthalmologicum Universale	Kyoto, Japan
	29-31	American Ophthalmological Society	Hot Springs, Virginia
OCTOBER	16-20	American College of Surgeons Clinical Congress	San Francisco
NOVEMBER (tentative)	5-9	Association of American Medical Colleges	New Orleans

1979

MAY	28-30	American Ophthalmological Society	Washington, D.C.
OCTOBER	22-26	American College of Surgeons Clinical Congress	Hot Springs, Virginia
NOVEMBER	4-8	Association of American Medical Colleges/Association of University Professors in Ophthalmology	Chicago

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Write: AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY
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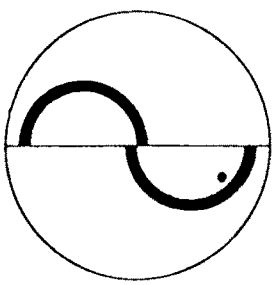
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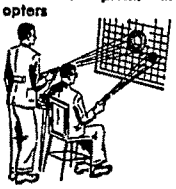
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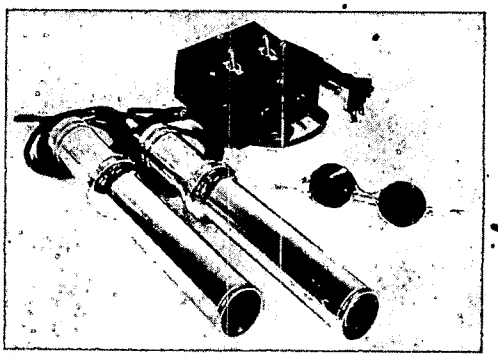
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2. DATE OF FILING: Oct. 1, 1975
3. FREQUENCY OF ISSUE: Monthly
3A. ANNUAL SUBSCRIPTION PRICE: $15.00
4. LOCATION OF KNOWN OFFICE OF PUBLICATION (Street, city, county, state and ZIP code) (Not printers): 233 East Ontario, Suite 1401, Chicago, Illinois 60611
5. LOCATION OF THE HEADQUARTERS OR GENERAL BUSINESS OFFICES OF THE PUBLISHERS (Not printers):

6. NAMES AND ADDRESSES OF PUBLISHER, EDITOR, AND MANAGING EDITOR
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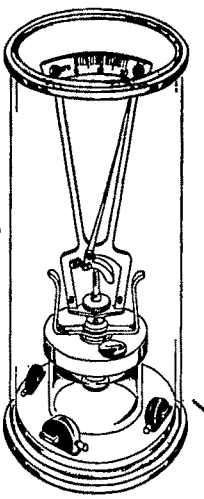
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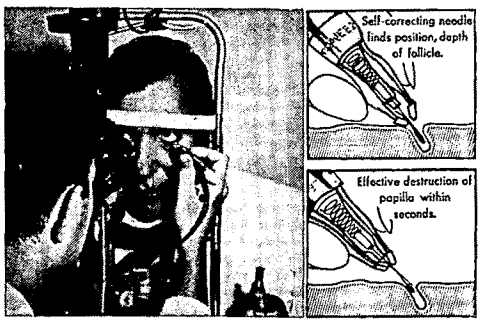
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WHEN THE DOCTOR DIES

You will probably need to know these items:

1. Social Security Number or Taxpayer's Identification Number
2. Accountant or Estate Planner: Name, address, phone number
3. Attorney: Name, address, phone number
4. Employee(s): Name(s), address(es), phone number(s), details of termination of services
5. Insurance Agent (and/or Estate Planning Manager): Name, address, phone number
6. Stockbroker: Name, address, phone number
7. Trust (if established): Name of Trustee, address, phone number, name of bank's representative, phone, extension if the trustee is a bank
8. Will: Location, location of any codicils
9. Home: Location of deed, mortgage papers, etc.
10. Office: Location of deed or lease, mortgage papers, duration of lease or mortgage, provision for settling in event of death
11. Other real estate: Location(s) of deed(s) or mortgage paper(s)
12. Life Insurance: Location of policies
13. Other Insurance: Location of policies
14. Temporary coverage of the Practice: Name, address and phone number of an associate
15. Securities: Location of policies
16. Current unpaid bills: Location
17. Outstanding obligations: Notes, mortgages, pledges, charge accounts, credit checking accounts, etc. Details
18. Safety Deposit Box(es): Location(s), number(s), location of keys
19. Savings Account(s): Location(s) of passbook(s)
20. Checking Account(s): Location(s), location(s) of checkbook(s)
21. Financial Records: Location
22. Cash: Location of receipts, unbanked cash, source of cash for immediate needs
23. Tax Information: Location
24. Accounts Receivable: Location, the Doctor's views on collecting current and delinquent bills
25. Notes, loans, mortgages, etc., due from others: Location of items
26. Notifying patients: Method preferred by the doctor, location of appointment book
27. Notification: Hospital(s)—(Administrator), phone numbers: colleagues, phone numbers, Societies, etc., phone numbers
28. Veterans Administration: Branch of Service, date of discharge, service number, VA number(s), location of discharge papers
29. Blue Cross, etc.: Policy numbers of Blue Cross, Blue Shield and other Health Insurance (see later discussion)
30. Narcotics: Location of drugs, tax stamp, narcotics ledger, narcotics order book
31. Equipment (major): Purchase price, sales outlet
32. The Doctor's views on disposition of property, securities, anticipated income, etc.
33. Birth and Marriage Records: Location
34. Citizenship Papers (if applicable): Location

In addition to the foregoing but subject to the rights and duties of the Executor or Administrator, you may become involved with the following:

I. Probate of the Will: Your attorney will do this.

II. Disposition of narcotics, drug samples and medications. You should contact your Regional Office of the Bureau of Narcotics and Dangerous Drugs, U.S. Department of Justice, requesting disposition forms which must be completed and returned.

III. Patient Records:

A. These are important and confidential records which should be carefully preserved. Apparently there is no set limit of time specified by law.

B. The contents of such records should be disclosed to another physician only if the patient so requests. Such a request should be in writing and should be retained with the records. Normally, the records are confidential and diagnostic information in them should not be disclosed directly to the patient because of the risk that he might misinterpret them.

C. All patients' medical records should be kept for a minimum of ten years. Records of patients who were minors when treated should be preserved until two years after the patient reaches twenty-one. When possible, records should be kept for twenty-five years. It should be kept in mind that requirements for the retention of medical records may vary from state to state. Accordingly, before any medical records are destroyed or disposed of, local requirements should be verified with either the attorney for the estate or the local medical society. Financial records should be kept for five years, which is the statute of limitations on such information.

IV. Telephone: If there is an answering service, this can be a very helpful way of notifying patients of the Doctor's death with possible suggestions regarding their continued care. It is suggested that this service be retained for at least a month.

V. Notifying patients: Perhaps a simple sign on the office door "Call ———————— (office phone number)" will relieve you of the burden of contact with most of the patients and the answering service can take care of the matter.

If the physician's secretary is retained temporarily she might perform this service by being present during usual office hours. She also could notify patients with future appointments during this time.

VI. Taxes: The accountant and/or attorney should take care of all of this in connection with the financial records.

VII. Stopping advertising mail: It may take a year for knowledge of the Doctor's death to reach all the mailing lists; there is no central clearing office. You may perhaps choose to let it run out in this fashion, or you may write "Deceased return to sender" on each piece and mail it back. While the latter course might entail some effort initially, it will rapidly and effectively cut off the flow.

VIII. Insurance Agent and/or Trustee: A preliminary brief conference might be in order to settle the question of immediate funds, documents to be located, and arrangements for a later, detailed conference. Prompt notification of such people is important.

IX. Consideration of Sale of Practice: If the practice is to be sold, with or without real estate, relatively rapid action is advised, for it will quickly lose value. It can be advertised in the State Medical "Journal" and the "Journal" of the American Medical Association.

X. Real Estate: Except for practice-connected real estate, a hasty decision on sale or retention is not advised. It is hoped that the doctor has made known his views on this subject.

XI. Temporary coverage of patients:

A. Some arrangement with a colleague should be made immediately as regards patients in the hospital.

B. While not required, it would be a courtesy to be able to suggest a colleague to other patients.

XII. Insurance:

A. Malpractice Insurance: A refund on unused premiums may be possible. Find the policy and consult the local agent.

B. Liability and other Insurances: Certain policies issued with reference to the practice might have provisions for refund of unused premiums. Consult the issuing company or your insurance agent.

C. Health and Hospital Insurance: The survivor of a physician who had hospital or other health insurance under a group or family plan may keep such insurance, but it should be transferred to individual instead of family policies, unless you have dependent children.

XIII. Veterans Administration: If the Doctor was a Veteran, notify the Veterans Administration with the indicated information and apply for deserved benefits. Help with this can be had through the Veteran's Service Officer of the Doctor's county or district, or the Veterans Administration Regional Office. In this connection, save the Doctor's discharge papers permanently. It is possible that Pensions or other forms of remuneration may be provided in the future.

XIV. Social Security: Nearly all physicians are now covered by the Social Security Act. Visit the Social Security Office serving your area to find out what benefits are available to you. Be certain to have the Doctor's Social Security or Taxpayer Identification Number.

XV. Automobile(s): Title, if in Doctor's name, can be transferred with assistance of an automobile club, if a member, or through the Department of Motor Vehicles. Be sure insurance coverage is retained.

XVI. Equipment: It is best disposed of as part of the practice, if possible. Otherwise, it might be possible to obtain an estimate of value from one of the reputable equipment vendors and then sold either privately, through an advertisement in the State Medical "Journal" or to a dealer of used equipment. One of the Doctor's colleagues can give you the names of the major supply dealers serving your area.

XVII. Current bills: These must be paid, but not until the court has approved the Executor or appointed the Administrator of the Doctor's estate.

XVIII. Magazine subscriptions: Those purchased for office use might be checked for possible stoppage and subscription refund if you do not wish to continue them.

XIX. Dues: There is ordinarily no refund on Medical Society dues unless hardship exists.

XX. Securities: It is worth noting that Securities can be used as collateral for loans to meet financial needs. This may be preferable to selling the securities.

The American Society of Internal Medicine has learned with regret of the Doctor's death. We wish to extend our condolences. We realize that you will have many tasks in connection with settlement of the estate. To assist you the Society has prepared this pamphlet.

It should be pointed out that many of the items appearing herein are matters which, technically, will be the professional responsibility of the Executor (if the Doctor died with a Will) or the Administrator (if the Doctor died without a Will). However, the information contained herein may prove to be helpful not only to the person having this responsibility but also to the Doctor's survivor. We recommend that the survivor discuss the contents of this pamphlet with the Executor or Administrator of the Doctor's estate as soon as possible.

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The manuscript should be arranged in the following order:

1. Title page (with footnotes)
2. Text and summary
3. Acknowledgments
4. References
5. Tables
6. Legends for figures

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TITLE PAGE The title page should be numbered page 1 and contain the running (abbreviated) heading, the title, each author's name and highest degree, and the city and state where the work was carried out. The institution and the organization(s) sponsoring the study should be credited in a footnote. A second footnote should give the name and mailing address of the author to whom correspondence should be directed. Each page after the title page should show the page number, senior author's name, and running title in the upper righthand corner.

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Following a description of material and methods, the results of the study should be given. A section devoted to discussion should follow. The discussion should relate directly to the topic of the paper.

Summary—Each paper must have a summary that describes the content of the paper in no more than 150 words. The author should state precisely what was accomplished, and avoid generalities.

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Suggestions to Authors — CONT.

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1. Terry, T. L.: Extreme prematurity and ibroblastic overgrowth of persistent vas- ular sheath behind each crystalline lens. Am. J. Ophth. 25:203, 1942.

2. Reese, A. B.: Tumors of the Eye, 2nd d. New York, Hoeber, 1964, p. 91.

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TABLES Each table must be titled, num- bered with an arabic numeral, and cited in he text. The title should appear directly below the designation, Table 1, and well below the title, a double rule (two parallel ines) should span the width of the table. Between this double rule and a similar, ull-width single rule, a heading must be iven for each column. Smaller rules span- ing several columns can be used to sep- rate main (several-column) headings from ubheadings, if necessary. No other vertical r horizontal lines should be used. Each able should be double-spaced, and nothing n the table should be underscored.

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